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(60) Parent Application or Grant AMERICAN CYANAMID COMPANY [/]; O. WISSNER, Allan [/]; O. TSOU, Hwei-Ru [/]; O. BERGER, Dan, Maarten [/]; O. FLOYD, Middleton, Brawner, Jr. [/]; O. HAMANN, Philip, Ross [/]; O. ZHANG, Nan [/]; O. FROST, Philip [/]; O. MILOWSKY, Arnold, S. ; O.			
(54) Title: SUBSTITUTED 3-CYANOQUINOLINES AS PROTEIN TYROSINE KINASES INHIBITORS (54) Titre: INHIBITEURS DE PROTEINES DE TYPE TYROSINE KINASES A BASE DE 3-CYANOQUINOLINES SUBSTITUEES			
(57) Abstract <p>This invention provides compounds of formula (1), wherein R₁, G₁, G₂, R₄, Z, X and n are defined herein, or a pharmaceutically acceptable salt thereof, which are useful as antineoplastic agents and in the treatment of polycystic kidney disease.</p>			
(57) Abrégé <p>La présente invention concerne des composés représentés par la formule générale (1) ou certains de leurs sels pharmaceutiquement admis. Dans cette formule, R₁, G₁, G₂, R₄, Z, X et n sont tels que décrits dans cette demande internationale. Ces composés, ou les sels considérés, conviennent d'une part comme antinéoplasiques et d'autre part pour le traitement de la polykystose rénale.</p>			

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(51) International Patent Classification ⁷ : C07D 215/54, A61K 31/47, C07D 401/12, 417/12, 215/56, 401/04, 491/10, 405/12, 413/12 // (C07D 491/10, 317:00, 211:00)		A1	(11) International Publication Number: WO 00/18740 (43) International Publication Date: 6 April 2000 (06.04.00)
<p>(21) International Application Number: PCT/US99/22056</p> <p>(22) International Filing Date: 22 September 1999 (22.09.99)</p> <p>(30) Priority Data: 09/162,289 29 September 1998 (29.09.98) US</p> <p>(71) Applicant: AMERICAN CYANAMID COMPANY [US/US]; Five Giraldi Farms, Madison, NJ 07940-0874 (US).</p> <p>(72) Inventors: WISSNER, Allan; 31 Wood Avenue, Ardsley, NY 10502 (US). TSOU, Hwei-Ru; 7 Beverly Place, New City, NY 10956 (US). BERGER, Dan, Maarten; 6 Iron Drive, New City, NY 10956 (US). FLOYD, Middleton, Bruwner, Jr.; 5 Babbling Brook Drive, Suffern, NY 10901 (US). HAMANN, Philip, Ross; 9 Alice Street, Germerville, NY 10923 (US). ZHANG, Nan; 9 New Street, Apartment 2C, Eastchester, NY 10709 (US). FROST, Philip; 4 Emerson Court, Morris Township, NJ 07960 (US).</p> <p>(74) Agents: MILOWSKY, Arnold, S.; American Home Products Corporation, Patent Law Dept.-2B, One Campus Drive, Parsippany, NJ 07054 (US) et al.</p>		<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	
<p>(54) Title: SUBSTITUTED 3-CYANOQUINOLINES AS PROTEIN TYROSINE KINASES INHIBITORS</p> <p>(57) Abstract</p> <p>This invention provides compounds of formula (1), wherein R₁, G₁, G₂, R₄, Z, X and n are defined herein, or a pharmaceutically acceptable salt thereof, which are useful as antineoplastic agents and in the treatment of polycystic kidney disease.</p> <p style="text-align: center;"></p> <p style="text-align: right;">(1)</p>			

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Description

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SUBSTITUTED 3-CYANOQUINOLINES AS PROTEIN TYROSINE KINASES INHIBITORS

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BACKGROUND OF THE INVENTION

This invention relates to certain substituted 3-cyano quinoline compounds as well as the pharmaceutically acceptable salts thereof. The compounds of the present invention inhibit the action of certain growth factor receptor protein tyrosine kinases (PTK) and other protein kinases thereby inhibiting the abnormal growth of certain cell types. The compounds of this invention are therefore useful for the treatment of certain diseases that are the result of deregulation of these PTKs. The compounds of this invention are anti-cancer agents and are useful for the treatment of cancer in mammals. In addition, the compounds of this invention are useful for the treatment of polycystic kidney disease in mammals. This invention also relates to the manufacture of said 3-cyano quinolines, their use for the treatment of cancer and polycystic kidney disease, and the pharmaceutical preparations containing them.

Protein tyrosine kinases are a class of enzymes that catalyze the transfer of a phosphate group from ATP to a tyrosine residue located on a protein substrate. Protein tyrosine kinases clearly play a role in normal cell growth. Many of the growth factor receptor proteins function as tyrosine kinases and it is by this process that they effect signaling. The interaction of growth factors with these receptors is a necessary event in normal regulation of cell growth. However, under certain conditions, as a result of either mutation or overexpression, these receptors can become deregulated; the result of which is uncontrolled cell proliferation which can lead to tumor growth and ultimately to the disease known as cancer [Wilks A.F., *Adv. Cancer Res.*, 60, 43 (1993) and Parsons, J.T.; Parsons, S.J., *Important Advances in Oncology*, DeVita V.T. Ed., J.B. Lippincott Co., Phila., 3 (1993)]. Among the growth factor receptor kinases and their proto-oncogenes that have been identified and which are targets of the compounds of this invention are the epidermal growth factor receptor kinase (EGF-R kinase, the protein product of the erbB oncogene), and the product produced by the erbB-2 (also referred to as the neu or HER2) oncogene. Since the phosphorylation event is a necessary signal for cell division to occur and since overexpressed or mutated kinases have been associated with cancer, an inhibitor of

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10 this event, a protein tyrosine kinase inhibitor, will have therapeutic value for the treatment of cancer and other diseases characterized by uncontrolled or abnormal cell growth. For example, overexpression of the receptor kinase product of the erbB-2 oncogene has been associated with human breast and ovarian cancers [Slamon, D. J.,

15 et. al., *Science*, 244, 707 (1989) and *Science*, 235 , 1146 (1987)]. Deregulation of EGF-R kinase has been associated with epidermoid tumors [Reiss, M., et. al., *Cancer Res.*, 51, 6254 (1991)], breast tumors [Macias, A., et. al., *Anticancer Res.*, 7, 459 (1987)], and tumors involving other major organs [Gullick, W.J., *Brit. Med. Bull.*, 47, 87 (1991)]. Because of the importance of the role played by deregulated receptor

20 kinases in the pathogenesis of cancer, many recent studies have dealt with the development of specific PTK inhibitors as potential anti-cancer therapeutic agents [some recent reviews: Burke, T.R., *Drugs Future*, 17, 119 (1992) and Chang, C.J.; Geahlen, R.L., *J. Nat. Prod.*, 55, 1529 (1992)]. The compounds of this invention inhibit the kinase activity of EGF-R and are therefore useful for treating certain

25 disease states, such as cancer, that result, at least in part, from deregulation of this receptor. The compounds of this invention are also useful for the treatment and prevention of certain pre-cancerous conditions, such as the growth of colon polyps, that result, at least in part, from deregulation of this receptor.

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35 It is also known that deregulation of EGF receptors is a factor in the growth of epithelial cysts in the disease described as polycystic kidney disease [Du J., Wilson P. D., *Amer. J. Physiol.*, 269(2 Pt 1), 487 (1995); Nauta J., et al., *Pediatric Research* , 37(6), 755 (1995); Gattone V.H., et al., *Developmental Biology*, 169(2), 504 (1995); Wilson P.D., et al., *Eur. J. Cell Biol.*, 61(1), 131, (1993)]. The compounds of this invention, which inhibit the catalytic function of the EGF receptors, are consequently

40 useful for the treatment of this disease.

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45 The mitogen-activated protein kinase (MAPK) pathway is a major pathway in the cellular signal transduction cascade from growth factors to the cell nucleus. The pathway involves kinases at two levels: MAP kinase kinases (MAPKK), and their substrates MAP kinases (MAPK). There are different isoforms in the MAP kinase

50 family. (For review, see Rony Seger and Edwin G. Krebs, FASEB, Vol. 9, 726, June 1995). The compounds of this invention can inhibit the action of two of these

10 kinases: MEK, a MAP kinase kinase, and its substrate ERK, a MAP kinase. MEK is activated by phosphorylation on two serine residues by upstream kinases such as members of the *raf* family. When activated, MEK catalyzes phosphorylation on a threonine and a tyrosine residue of ERK. The activated ERK then phosphorylates

15 5 and activates transcription factors in the nucleus, such as *fos* and *jun*, or other cellular targets with PXT/SP sequences. ERK, a p42 MAPK is found to be essential for cell proliferation and differentiation. Over-expression and/or over-activation of Mek or ERK has been found to be associated with various human cancers (For example,

20 Vimala S. Sivaraman, Hsien-yu Wang, Gerard J. Nuovo, and Craig C. Malbon, J.

25 10 Clin. Invest. Vol. 99, No. 7 April 1997). It has been demonstrated that inhibition of MEK prevents activation of ERK and subsequent activation of ERK substrates in cells, resulting in inhibition of cell growth stimulation and reversal of the phenotype of *ras*-transformed cells (David T. Dudley, Long Pang, Stuart J. Decker, Alexander J.

30 Bridges, and Alan R. Saltiel, PNAS, Vol. 92, 7686, August 1995). Since, as

35 15 demonstrated below, the compounds of this invention can inhibit the coupled action of MEK and ERK, they are useful for the treatment of diseases such as cancer which are characterized by uncontrolled cell proliferation and which, at least in part, depend on the MAPK pathway.

40 Epithelial Cell Kinase (ECK) is a receptor protein tyrosine kinase (RPTK)

45 20 belonging to the EPH (Erythropoietin Producing Hepatoma) family. Although originally identified as an epithelial lineage-specific tyrosine kinase, ECK has subsequently been shown to be expressed on vascular endothelial cells, smooth muscle cells, and fibroblasts. ECK is a type I transmembrane glycoprotein with the extracellular ligand-binding domain consisting of a cysteine-rich region followed by

50 25 three fibronectin type III repeats. The intracellular domain of ECK possesses a tyrosine kinase catalytic domain that initiates a signal transduction cascade reflecting the ECK function. ECK binds and is subsequently activated by its counter-receptor, Ligand for Eph-Related Kinase (LERK)-1, which is an immediate early response gene product readily inducible in a lineage-unrestricted manner with proinflammatory

55 30 cytokines such as IL-1 or TNF. Soluble LERK-1 has been shown to stimulate angiogenesis in part by stimulating ECK in a murine model of corneal angiogenesis.

Unlike their normal counterparts, tumor cells of various lineages constitutively express LERK-1 and this expression can further be upregulated by hypoxia and proinflammatory cytokines. Many of these tumor cells also express ECK at higher levels than their normal counterparts, thereby creating an opportunity for autocrine

stimulation via ECK : LERK-1 interaction. The increased expression of both ECK and LERK-1 has been correlated with the transformation of melanomas from the noninvasive horizontal phase of growth into very invasive vertically growing metastatic melanomas. Together, the ECK : LERK-1 interaction is believed to promote tumor growth via its tumor growth promoting and angiogenic effects. Thus, the inhibition of the ECK tyrosine kinase activity mediating signaling cascade induced by its binding and cross-linking to LERK-1 may be therapeutically beneficial in cancer, inflammatory diseases, and hyperproliferative disorders. As is shown below, the compounds of this invention inhibit the tyrosine kinase activity of ECK and are therefore useful for the treatment of the aforementioned disorders.

Growth of most solid tumors is dependent on the angiogenesis involving activation, proliferation and migration of vascular endothelial cells and their subsequent differentiation into capillary tubes. Angiogenization of tumors allows them access to blood-derived oxygen and nutrients, and also provides them adequate perfusion. Hence inhibiting angiogenesis is an important therapeutic strategy in not only cancer but also in a number of chronic diseases such as rheumatoid arthritis, psoriasis, diabetic retinopathy, age-related macular degeneration, and so on. Tumor cells produce a number of angiogenic molecules. Vascular Endothelial Growth Factor (VEGF) is one such angiogenic factor. VEGF, a homodimeric disulfide-linked member of the PDGF family, is an endothelial cell-specific mitogen and is known to cause profound increase in the vascular endothelial permeability in the affected tissues. VEGF is also a senescence-preventing survival factor for endothelial cells. Almost all nucleated tissues in the body possess the capability to express VEGF in response to various stimuli including hypoxia, glucose deprivation, advanced glycation products, inflammatory cytokines, etc. Growth-promoting angiogenic effects of VEGF are mediated predominantly via its signaling receptor Kinase insert Domain containing Receptor (KDR). The expression of KDR is low on most

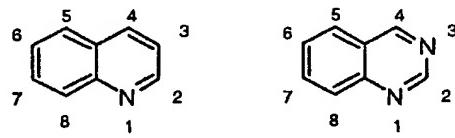
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endothelial cells; however, activation with angiogenic agents results in a significant upregulation of KDR on endothelial cells. Most angiogenized blood vessels express high levels of KDR. KDR is a receptor protein tyrosine kinase with an extracellular VEGF-binding domain consisting of 7 immunoglobulin-like domains and a cytoplasmic domain containing the catalytic tyrosine kinase domain split by a kinase-insert region. Binding to VEGF causes dimerization of KDR resulting in its autophosphorylation and initiation of signaling cascade. Tyrosine kinase activity of KDR is essential for mediation of its functional effects as a receptor for VEGF. Inhibition of KDR-mediated functional effects by inhibiting KDR's catalytic activity is considered to be an important therapeutic strategy in the treatment of angiogenized disease states including cancer. As is shown below, the compounds of this invention inhibit the tyrosine kinase activity of KDR and are therefore useful for the treatment of the aforementioned disease states.

In addition to the above utilities some of the compounds of this invention are useful for the preparation of other compounds of this invention.

The compounds of this invention are certain substituted 3-cyano quinolines. Throughout this patent application, the quinoline ring system will be numbered as indicated in the formula below; the numbering for the quinazoline ring system is also shown:



No 3-cyano quinolines have been reported that have biological activity as inhibitors of protein tyrosine kinases. A 3-cyano quinoline with a 4-(2-methyl anilino) substituent having gastric (H⁺/K⁺)-ATPase inhibitory activity at high concentrations has been described [Ife R.J., et al., *J. Med. Chem.*, 35(18), 3413 (1992)].

There are quinolines that do not have the 3-cyano substituent and, unlike the compounds of this invention, are unsubstituted at the 4-position but are reported to be inhibitors of protein tyrosine kinases [Gazit A., et al., *J. Med. Chem.*, 39(11), 2170

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(1996)]. A series of quinolines that have a 3-pyridyl substituent and no substituent at the 4-position have been described as inhibitors of platelet derived growth factor receptor kinase [Dolle R.E., et al., *J. Med. Chem.*, 372, 2627 (1994) and Maguire M.P., et al., *J. Med. Chem.*, 372, 129 (1994)]. The patent applications WO 96/09294 and WO-9813350 describe inhibitors of protein tyrosine kinases that include 4-anilino quinolines with a large variety of substituents on positions 5-8 but which must also have a hydrogen or fluorine atom at position 3. The US patent 5,480,883 describes quinoline derivatives that are inhibitors of protein tyrosine kinases but these derivatives do not have the unique combination of substituents, including the 3-cyano group, contained in the compounds of the present invention. The applications WO-9802434 and WO-9802438 describe quinoline derivatives that are tyrosine kinase inhibitors but these quinolines do not have the important 3-cyano substituent .

In addition to quinolines, certain quinazoline derivatives that are similar, in some respects, to the compounds of this invention are known to be inhibitors of protein tyrosine kinases. The application EP-520722 describes 4-anilinoquinazolines that contain simple substituents such as chloro, trifluoromethyl, or nitro groups at positions 5 to 8. The application EP-566226 is similar but with a much larger variety of substituents now allowed at positions 5 to 8. The application WO-9609294 describes compounds with similar substituents at positions 5 to 8 and with the substituent at to 4-position consisting of some polycyclic ring systems. Some simple substituted quinazolines are also described in the applications WO-9524190, WO-9521613, and WO-9515758. The applications EP-602851 and WO-9523141 cover similar quinazoline derivatives where the aryl group attached at position 4 can be a variety of heterocyclic ring structures. The application EP-635498 describes certain quinazoline derivatives that have alkenoylamino and alkynoylamino groups among the substituents at position 6 and a halogen atom at position 7. The application WO-9519774 describes compounds where one or more of the carbon atoms at positions 5-8 can be replaced with heteroatoms resulting in a large variety of bicyclic systems where the left-hand ring is a 5 and 6-membered heterocyclic ring; in addition, a variety of substituents are allowed on the left-hand ring. The application EP-682027-A1 describes certain pyrrolopyrimidine inhibitors of PTKs. The

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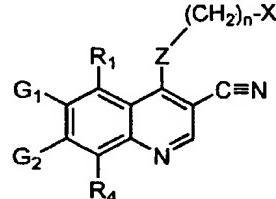
application WO-9519970 describes compounds in which the left-hand aromatic ring of the basic quinazoline structure has been replaced with a wide variety of different heterocyclic rings so that the resulting inhibitors are tricyclic. The application EP-635507 describes quinazolines where an additional 5 or 6-membered heterocyclic ring with optional substitution is fused at positions 5 and 6.

In addition to the aforementioned patent applications, a number of publications describe 4-anilinoquinazolines: Fry, D.W., et. al., *Science*, 265, 1093 (1994), Newcastle G.W., et. al., *J. Med. Chem.*, 38, 3482 (1995), and Bridges, A.J., et. al., *J. Med. Chem.*, 39, 267, (1996). There are no publications that describe 3-cyano quinolines as PTK inhibitors.

DESCRIPTION OF THE INVENTION

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This invention provides a compound of formula 1:



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wherein:

40 X is cycloalkyl of 3 to 7 carbon atoms, which may be optionally substituted with one or more alkyl of 1 to 6 carbon atom groups; or is a pyridinyl, pyrimidinyl, or

20 phenyl ring wherein the pyridinyl, pyrimidinyl, or phenyl ring may be
45 optionally mono-, di-, or tri-substituted with a substituent selected from the group consisting of halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxalkyl of 1-6 carbon atoms, halomethyl, alkoxyalkyl of 2-7 carbon atoms, alkanoyloxyethyl of 2-7
50 25 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms,

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hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, carboxyalkyl of 2-7 carbon atoms, carboalkoxyalkyl of 3-8 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-10 carbon atoms, N-alkylaminoalkoxy of 2-9 carbon atoms, N,N-dialkylaminoalkoxy of 3-10 carbon atoms, mercapto, and benzoylamino;

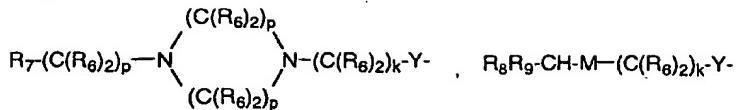
Z is -NH-, -O-, -S-, or -NR- ;

R is alkyl of 1-6 carbon atoms, or carboalkyl of 2-7 carbon atoms;

G₁, G₂, R₁, and R₄ are each, independently, hydrogen, halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkenyloxy of 2-6 carbon atoms, alkynyoxy of 2-6 carbon atoms, hydroxymethyl, halomethyl, alkanoyloxy of 1-6 carbon atoms, alkenoyloxy of 3-8 carbon atoms, alkynoyloxy of 3-8 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkenoyloxymethyl of 4-9 carbon atoms, alkynoyloxymethyl of 4-9 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, alkylsulphanyl of 1-6 carbon atoms, alkylsulphonyl of 1-6 carbon atoms, alkylsulfonamido of 1-6 carbon atoms, alkynylsulfonamido of 2-6 carbon atoms, alkynylsulfonamido of 2-6 carbon atoms, hydroxy, trifluoromethyl, trifluoromethoxy, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzyl, amino, hydroxyamino, alkoxyamino of 1-4 carbon atoms, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, N-alkylcarbamoyl, N,N-dialkylcarbamoyl, N-alkyl-N-alkenylamino of 4 to 12 carbon atoms, N,N-dialkenylamino of 6-12 carbon atoms, phenylamino, benzylamino,

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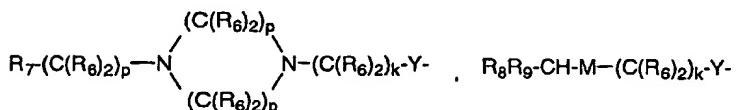


$R_7-(C(R_6)_2)_q-Y-$, $R_7-(C(R_6)_2)_p-M-(C(R_6)_2)_k-Y-$, or $Het-(C(R_6)_2)_q-W-(C(R_6)_2)_k-Y-$.

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with the proviso that either G₁ or G₂ or both G₁ and G₂ must be a radical selected from the group

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$$R'_7-(C(R_6)_2)_n-Y \dots R_7-(C(R_6)_2)_n-M-(C(R_6)_2)_k-Y \dots Het-(C(R_6)_2)_l-W-(C(R_6)_2)_k-Y \dots$$

or R_2-N- ;

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Y is a divalent radical selected from the group consisting of

35

$-(CH_2)_a-$, $-O-$, and $-N-$;

35

R₇ is -NR₆R₆, -J, -OR₆, -N(R₆)₃⁺ or -NR₆(OR₆);

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R'_7 is $-NR_6(OR_6)$, $-N(R_6)_3^+$, alkoxy of 1-6 carbon atoms, alkynoxy of 1-6 carbon

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atoms, N-alkyl-N-alkenylamino of 4 to 12 carbon atoms, N,N-dialkenylamino of 6-12 carbon atoms. N-alkyl-N-alkynylamino of 4 to 12 carbon atoms. N-alkenyl-N-

15 alkynylamino of 4 to 12 carbon atoms, or N,N-dialkynylamino of 6-12 carbon atoms with the proviso that the alkenyl or alkynyl moiety is bound to a nitrogen or oxygen atom through a saturated carbon atom:

M is $>\text{NR}_6$, $-\text{O}-$, $>\text{N}-(\text{C}(\text{R}_6)_2)_n\text{NR}_6\text{R}_6$, or $>\text{N}-(\text{C}(\text{R}_6)_2)_n-\text{OR}_6$;

W is >NR_6 , -O- or is a bond:

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20 Het is a heterocycle selected from the group consisting of morpholine, thiomorpholine, S-oxide thiomorpholine, S,S-dioxide

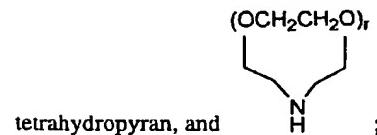
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10 piperidine, pyrrolidine, aziridine, pyridine, imidazole, 1,2,3-triazole, 1,2,4-triazole, thiazole, thiazolidine, tetrazole, piperazine, furan, thiophene, tetrahydrothiophene, tetrahydrofuran, dioxane, 1,3-dioxolane,

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20 wherein the heterocycle is optionally mono- or di-substituted on carbon or nitrogen with R₆, optionally mono- or di-substituted on carbon with hydroxy, -N(R₆)₂, or -OR₆, optionally mono or di-substituted on carbon with the mono-valent radicals -(C(R₆)₂)_sOR₆ or -(C(R₆)₂)_sN(R₆)₂, or optionally 25 mono or di-substituted on a saturated carbon with divalent radicals -O- or -O(C(R₆)₂)_sO-;

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30 R₆ is hydrogen, alkyl of 1-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 1-6 carbon atoms, carboalkyl of 2-7 carbon atoms, carboxyalkyl (2-7 carbon atoms), phenyl, or phenyl optionally substituted with one or more halogen, alkoxy of 1-6 carbon atoms,

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15 trifluoromethyl, amino, alkylamino of 1-3 carbon atoms, dialkylamino of 2-6 carbon atoms, nitro, cyano, azido, halomethyl, alkoxy methyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, carboxyl, carboalkoxy of 2-7 carbon atoms, phenoxy, phenyl, 40 thiophenoxy, benzoyl, benzyl, phenylamino, benzylamino, alkanoylamino of 20 1-6 carbon atoms, or alkyl of 1-6 carbon atoms;

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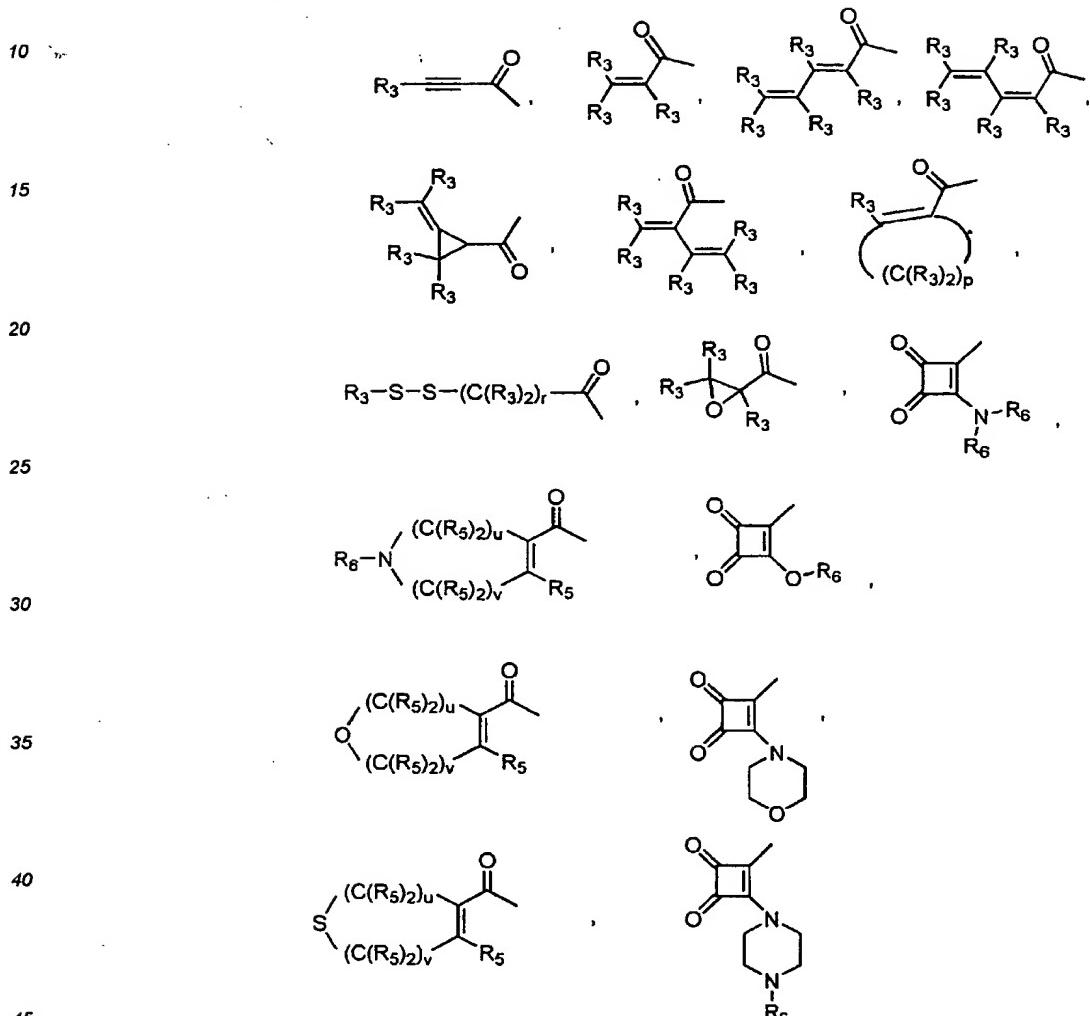
R₂, is selected from the group consisting of

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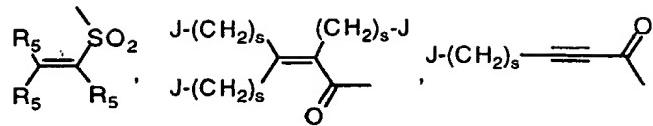
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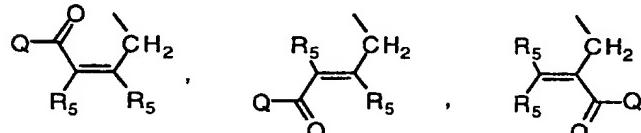
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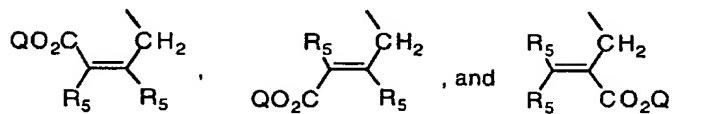
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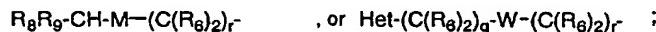
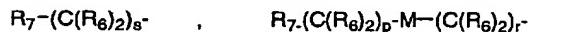
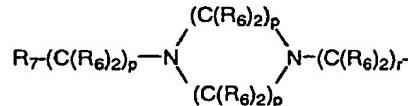
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R₃ is independently hydrogen, alkyl of 1-6 carbon atoms, carboxy, carboalkoxy of

5 1-6 carbon atoms, phenyl, carboalkyl of 2-7 carbon atoms,

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, or Het-(C(R₆)₂)_q-W-(C(R₆)₂)_r ;

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with the proviso that at least one of the R₃ groups is selected from the group

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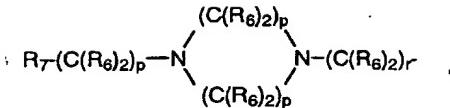
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- 13 -



$$R'_7-(C(R_6)_2)_s- \quad . \quad R_7-(C(R_6)_2)_p-M-(C(R_6)_2)_r-$$

15

$R_8R_9-CH-M-(C(R_6)_2)_r$, or $Het-(C(R_6)_2)_q-W-(C(R_6)_2)_r$;

20 1-6 carbon atoms, phenyl, carboalkyl of 2-7 carbon atoms,
5

20

$$\text{R}_7(\text{C}(\text{R}_6)_2)_p - \text{N} \begin{array}{c} (\text{C}(\text{R}_6)_2)_p \\ \swarrow \quad \searrow \\ (\text{C}(\text{R}_6)_2)_p \end{array} \text{N} - (\text{C}(\text{R}_6)_2)_r -$$

$$R_7-(C(R_6)_2)_s \quad . \quad R_7-(C(R_6)_2)_p-M-(C(R_6)_2)_r$$

30

R₈R₉-CH-M-(C(R₆)₂)_r- , or Het-(C(R₆)₂)_q-W-(C(R₆)₂)_r ;

R₈, and R₉ are each, independently, -(C(R₆)₂)_rNR₆R₆, or -(C(R₆)₂)_rOR₆;

J is independently hydrogen, chlorine, fluorine, or bromine;

35

10 Q is alkyl of 1-6 carbon atoms or hydrogen;

$$a = 0 \text{ or } 1;$$

g = 1-6;

40

$$k = 0.4;$$

n is 0-1;

15 p = 2-4;

$q=0-4;$

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16

58

$\mu = 0.4$ and $\nu = 0.4$, wherein the sum of $\mu + \nu$ is 2.4.

20

20 or a pharmaceutically acceptable salt thereof

provided that

- 14 -

when R₆ is alkenyl of 2-7 carbon atoms or alkynyl of 2-7 carbon atoms, such
10 alkenyl or alkynyl moiety is bound to a nitrogen or oxygen atom
through a saturated carbon atom;

and further provided that

- 15 5 when Y is -NR₆- and R₇ is -NR₆R₆, -N(R₆)₃⁺, or -NR₆(OR₆), then g = 2-6;
when M is -O- and R₇ is -OR₆, then p = 1-4;
when Y is -NR₆-, then k = 2-4;
when Y is -O- and M or W is -O-, then k = 1-4;
20 10 when W is not a bond with Het bonded through a nitrogen atom, then q = 2-4;
and when W is a bond with Het bonded through a nitrogen atom and Y is -O-
or -NR₆-, then k = 2-4 .

The pharmaceutically acceptable salts are those derived from such organic and
inorganic acids as: acetic, lactic, citric, tartaric, succinic, maleic, malonic, gluconic,
30 15 hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, and
similarly known acceptable acids.

The alkyl portion of the alkyl, alkoxy, alkanoyloxy, alkoxyethyl, alkanoyloxyethyl, alkylsulphanyl, alkylsulphonyl, aminoalkyl, N-alkylaminoalkyl, N,N-dialkylaminoalkyl, N-alkylaminoalkoxy, N,N-dialkylaminoalkoxy, alkyl-35 20 sulfonamido, carboalkoxy, carboalkyl, carboxyalkyl, carboalkoxyalkyl, alkanoylamino, N-alkylcarbamoyl, and N,N-dialkylcarbamoyl substituents include both straight chain as well as branched carbon chains. The alkenyl portion of the
40 25 alkenyl, alkenoyloxyethyl, alkenyloxy, alkenylsulfonamido, substituents include both straight chain as well as branched carbon chains and one or more sites of unsaturation and all possible configurational isomers. The alkynyl portion of the
45 30 alkynyl, alkynoyloxyethyl, alkynylsulfonamido, alkynyoxy, substituents include both straight chain as well as branched carbon chains and one or more sites of unsaturation. Carboxy is defined as a -CO₂H radical. Carboalkoxy of 2-7 carbon atoms is defined as a -CO₂R" radical, where R" is an alkyl radical of 1-6 carbon atoms. Carboxyalkyl is defined as a -HO₂C-R"" radical where R"" is a divalent alkyl

- 15 -

radical of 1-6 carbon atoms. Carboalkoxyalkyl is defined as a R"O₂C-R"- radical where R" is a divalent alkyl radical and where R" and R"" together have 2-7 carbon atoms. Carboalkyl is defined as a -COR" radical, where R" is an alkyl radical of 1-6 carbon atoms. Alkanoyloxy is defined as a -OCOR" radical, where R" is an alkyl

5 radical of 1-6 carbon atoms. Alkanoyloxymethyl is defined as R"CO₂CH₂- radical, where R" is an alkyl radical of 1-6 carbon atoms. Alkoxymethyl is defined as R"OCH₂- radical, where R" is an alkyl radical of 1-6 carbon atoms. Alkylsulphinyl is

10 defined as R"SO- radical, where R" is an alkyl radical of 1-6 carbon atoms. Alkylsulphonyl is defined as R"SO₂- radical, where R" is an alkyl radical of 1-6

15 carbon atoms. Alkylsulfonamido, alkenylsulfonamido, alkynylsulfonamido are defined as R"SO₂NH- radical, where R" is an alkyl radical of 1-6 carbon atoms, an

20 alkenyl radical of 2-6 carbon atoms, or an alkynyl radical of 2-6 carbon atoms, respectively. N-alkylcarbamoyl is defined as R"NHCO- radical, where R" is an alkyl radical of 1-6 carbon atoms. N,N-dialkylcarbamoyl is defined as R" R'NCO- radical,

25 15 where R" is an alkyl radical of 1-6 carbon atoms, R' is an alkyl radical of 1-6 carbon atoms and R', and R" may be the same or different . When X is substituted, it is preferred that it is mono-, di-, or tri-substituted, with monosubstituted being most preferred. It is preferred that of the substituents R1 and R4, at least one is hydrogen and it is most preferred that both be hydrogen. It is also preferred that X is a phenyl

30 20 ring, Z is -NH-, and n = 0.

Het is a heterocycle, as defined above which may be optionally mono- or di-substituted with R₆ on carbon or nitrogen, optionally mono- or di-substituted on carbon with hydroxy, -N(R₆)₂, or -OR₆, optionally mono or di-substituted on carbon with -(C(R₆)₂)_sOR₆ or -(C(R₆)₂)_sN(R₆)₂ . and optionally mono or di-

40 25 substituted on a saturated carbon with divalent radicals -O- or -O(C(R₆)₂)_sO- (carbonyl and ketal groups , respectively); in some cases when Het is substituted with -O- (carbonyl), the carbonyl group can be hydrated. Het may be bonded to W when q = 0 via a carbon atom on the heterocyclic ring, or when Het is a nitrogen containing heterocycle which also contains a saturated carbon-nitrogen bond, such heterocycle

45 30 may be bonded to carbon, via the nitrogen when W is a bond. When q = 0 and Het is

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- 16 -

10 a nitrogen containing heterocycle which also contains an unsaturated carbon-nitrogen bond, that nitrogen atom of the heterocycle may be bonded to carbon when W is a bond and the resulting heterocycle will bear a positive charge. When Het is substituted with R₆, such substitution may be on a ring carbon, or in the case of a

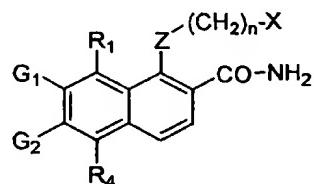
15 nitrogen containing heterocycle, which also contains a saturated carbon-nitrogen, such nitrogen may be substituted with R₆ or in the case of a nitrogen containing heterocycle, which also contains an unsaturated carbon-nitrogen, such nitrogen may be substituted with R₆ in which case the heterocycle will bear a positive charge.

20 Preferred heterocycles include pyridine, 2,6-disubstituted morpholine, 2,5-disubstituted thiomorpholine, 2-substituted imidazole, substituted thiazole, thiazolidine, N-substituted imidazole, N-substituted 1,4-piperazine, N-substituted piperadine, dioxane, 1,3-dioxolane, and N-substituted pyrrolidine.

25 The compounds of this invention may contain one or more asymmetric carbon atoms; in such cases, the compounds of this invention include the individual diastereomers, the racemates, and the individual R and S enantiomers thereof. Some of the compounds of this invention may contain one or more double bonds; in such cases, the compounds of this invention include each of the possible configurational isomers as well as mixtures of these isomers.

35 20 The compounds having formula 1 and their salts may be prepared by a process which comprises

40 45 (a) reacting a compound having the formula



50 25 where R₁, G₁, G₂, R₄, Z, n and X are as defined above with a dehydrating agent so as to convert the aminocarbonyl group into a cyano group, or

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- 17 -

(b) reacting a compound having the formula



or a salt thereof with a compound having the formula

5 where Q is a leaving group and A₁, A₂ and A₃ are such that A₁-NA₂-A₃ is a compound conforming with formula 1; or

(c) reacting a compound having the formula



10 or a salt thereof with a compound having the formula

25 where Q is as defined above and A₄ and A₅ are such that A₄-O-A₅ is a compound conforming with formula 1; or

30 15 (d) adding an acid to a compound having formula 1 so that an acid addition salt is prepared.

35 The preparation of the compounds and intermediates of this invention encompassed by Formula 5 is described below in Flowsheet 1 where Z and n are as

40 20 described above and X' is cycloalkyl of 3 to 7 carbon atoms, which may be optionally substituted with one or more alkyl of 1 to 6 carbon atom groups; or is a pyridinyl, pyrimidinyl, or phenyl ring wherein the pyridinyl, pyrimidinyl, or phenyl ring may be optionally mono-, di-, or tri-substituted with a substituent selected from the group consisting of halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms,

45 25 alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxyethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino,

50 30 alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms,

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- 18 -

alkynoylamino of 3-8 carbon atoms, carboxyalkyl of 2-7 carbon atoms, aminomethyl, N-alkylaminomethyl of 2-7 carbon atoms, N,N-dialkylaminomethyl of 3-7 carbon atoms, mercapto, and benzoylamino;

R_{1'}, R_{2'}, R_{3'}, and R_{4'} are each, independently, hydrogen, halogeno, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkenyloxy of 2-6 carbon atoms, alkynyoxy of 2-6 carbon atoms, halomethyl, alkoxyimethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, alkylsulphinyl of 1-6 carbon atoms, alkylsulphonyl of 1-6 carbon atoms, alkylsulfonamido of 1-6 carbon atoms, trifluoromethyl, cyano, nitro, carboxy, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzyl, alkoxyamino of 1-4 carbon atoms, dialkylamino of 2 to 12 carbon atom, N,N-dialkylaminoalkyl of 3-14 carbon atoms, phenylamino, benzylamino, N-alkylcarbamoyl of 1-6 carbon atoms, N,N-dialkylcarbamoyl of 2-12 carbon atoms. According to the sequence of reaction outlined in flowsheet 1, a quinoline-3-carboxylic acid ester of Formula 2 is hydrolyzed with base to furnish a carboxylic acid of Formula 3. The carboxylic acid group of 3 is converted to an acyl imidazole by heating it with carbonyldiimidazole in an inert solvent such as dimethylformamide (DMF) followed by the addition of ammonia to give the amide 4. Dehydration of the amide functional group with a dehydrating agent such as trifluoroacetic anhydride in pyridine, phosphorous pentoxide in an inert solvent, or the like gives the 3-cyano quinolines, 5, of this invention. In those cases where any of the intermediates have an asymmetric carbon atom, they can be used as the racemate or as the individual R or S enantiomers in which case the compounds of this invention will be in the racemic or R and S optically active forms, respectively. The quinoline-3-carboxylic acid esters of Formula 2, the quinoline-3-carboxylic acids of Formula 3, and the quinoline-3-carboxylic amides of Formula 4 needed to prepare the compounds of this invention are either already known to the art or can be prepared by procedures known in the art as detailed in the following references:

Sarges, Reinhard; Gallagher, Andrea; Chambers, Timothy J.; Yeh, Li An, *J. Med. Chem.*, 36, 2828 (1993); Savini, Luisa; Massarelli, Paola; Pellerano, Cesare; Bruni, Giancarlo, *Farmaco*, 48(6), 805 (1993); Ife, Robert J.; Brown, Thomas H.; Keeling,

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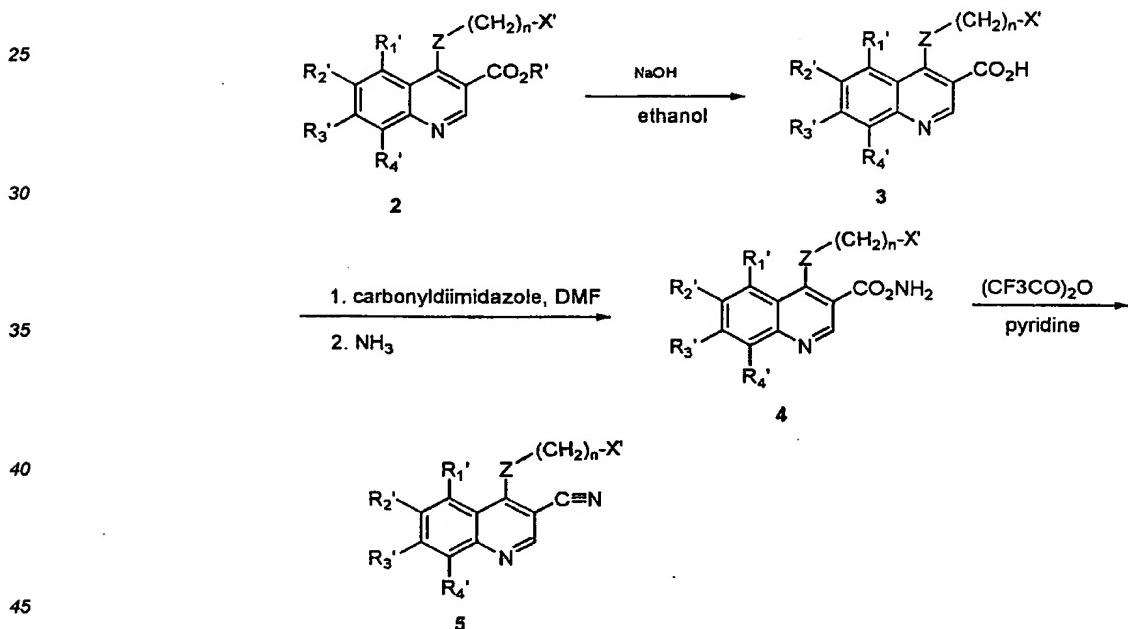
- 19 -

10 David J.; Leach, Colin, *J. Med. Chem.*, 35, 3413 (1992); Hanifin, J. William;
 Capuzzi, Rosemary; Cohen, Elliott, *J. Med. Chem.*, 12(5), 1096 (1969); Marecki,
 Paul E.; Bambury, Ronald E., *J. Pharm. Sci.*, 73(8), 1141 (1984); Pellerano, C.;
 Savini, L.; Massarelli, P.; Bruni, G.; Fiaschi, A. I., *Farmaco*, 45(3), 269, (1990);

15 5 Marecki, Paul E.; Bambury, Ronald E., *J. Pharm. Sci.*, 73(8), 114 (1984); patent
 application WO 8908105; US patent 4343804; US patent 3470186.

FLOW SHEET 1

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The preparation of the compounds of this invention encompassed by Formula 12 is described below in Flowsheet 2 where X, Z, n, R₁, G₁, G₂, and R₂ are as described

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- 20 -

above. The substituted aniline of Formula 6 is heated with or without a solvent with the reagent 7 to give intermediate 8 as a mixture of isomers. Thermolysis of 8 in a high boiling solvent such as diphenyl ether at 200-350°C gives the 3-cyano quinolones of Formula 9; these intermediates may also exist in the 4-hydroxy quinoline tautomeric form. In those cases where R₁ is a hydrogen atom, the intermediates 9 may be formed as a mixture of two regioisomers. These isomers can be separated by methods well known in the art including, but not limited to, fractional crystallization and chromatographic methods. The separated isomers can then be converted separately to the compounds of the invention. Alternatively, the isomers can be separated at a later stage of the synthesis. Heating compounds 9 with or without solvent with a chlorinating agent such as phosphorous oxychloride or phosphorous pentachloride gives the 4-chloro-3-cyano quinolines of Formula 10. Condensation of 10 with a nucleophilic amine, aniline, mercaptan, thiophenol, phenol, or alcohol reagent of Formula 11 gives the 3-cyano quinolines intermediates of Formula 12; this condensation can be accelerated by heating the reaction mixture or by using basic catalysts such as trialkylamines, sodium hydride in an inert solvent, sodium or potassium alkoxides in an alcohol solvents, and the like. In those cases where the substituents may contribute an asymmetric carbon atom, the intermediates can be used as the racemate or as the individual R or S enantiomers in which case the compounds of this invention will be in the racemic or R and S optically active forms, respectively. In cases where the substituents may contribute more than one asymmetric carbon atoms, diastereomers may be present; these can be separated by methods well known in the art including, but not limited to, fractional crystallization and chromatographic methods. In those cases where R₁, G₂, G₃, and R₄ moieties contain primary or secondary amino groups, the amino groups may first have to be used in protected form prior to reaction with reagent 7. Suitable protecting groups include, but are not limited to, tert-butoxycarbonyl (BOC) and benzyloxycarbonyl (CBZ) protecting groups. The former protecting group can be removed from the final products of Formula 12 by treatment with an acid such as trifluoroacetic acid while the latter protecting group can be removed by catalytic hydrogenation. In those cases where the R₁, G₂, G₃, and R₄ moieties contain hydroxyl groups, the hydroxyl groups

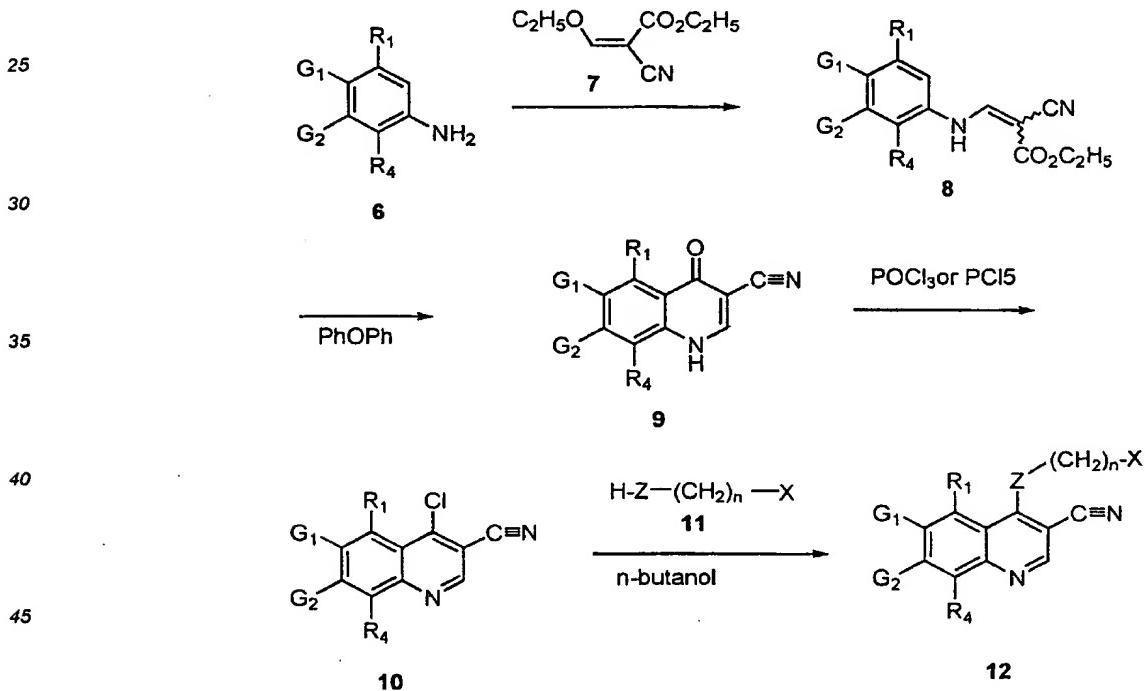
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may first have to be used in protected form prior to reaction with reagent 7. Suitable protecting groups include, but are not limited to, t-butyldimethylsilyl, tetrahydro-pyranyl, or benzyl protecting groups. The first two protecting groups can be removed from the final products of formula 12 by treatment with an acid such as acetic acid or hydrochloric acid while the latter protecting group can be removed by catalytic hydrogenation.

FLOWSHEET 2

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- 22 -

The preparation of intermediate 15 (identical to intermediate 9 of Flowsheet 2) can also be prepared as described below in Flowsheet 3. Heating the substituted aniline of Formula 13 with dimethylformamide dimethyl acetal with or without a solvent gives intermediates for Formula 14. The reaction of 14 with the lithium anion of acetonitrile prepared using a base such as n-butyl lithium or the like in an inert solvent gives the 3-cyano quinolones, 15, or the 3-cyano-4-hydroxy quinoline tautomers thereof which can be converted to the compounds of this invention. In those cases where R₁, G₂, G₃, and R₄ moieties contain primary or secondary amino groups, the amino groups may first have to be used in protected form. Suitable protecting groups include, but are not limited to, tert-butoxycarbonyl (BOC) and benzyloxycarbonyl (CBZ) protecting groups. The former protecting group can be removed from the final products of Formula 15 by treatment with an acid such as trifluoroacetic acid while the latter protecting group can be removed by catalytic hydrogenation. In those cases where the R₁, G₂, G₃, and R₄ moieties contain hydroxyl groups, the hydroxyl groups may first have to be used in protected form. Suitable protecting groups include, but are not limited to, t-butyldimethylsilyl, tetrahydropyranyl, or benzyl protecting groups. The first two protecting groups can be removed from the final products of formula 15 by treatment with an acid such as acetic acid or hydrochloric acid while the latter protecting group can be removed by catalytic hydrogenation.

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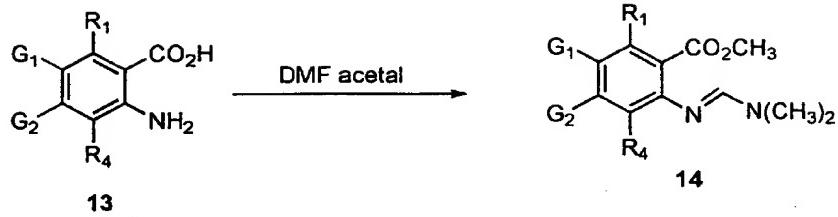
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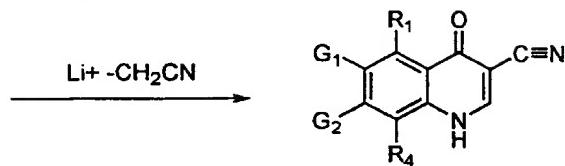
FLOWSHEET 3

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- 35 5 The preparation of the compounds of this invention encompassed by Formula 24 is described below in Flowsheet 4 wherein R₁, G₂, R₄, Z, n, and X are defined. R₁₀ is alkyl of 1-6 carbon atoms (preferably isobutyl). R_{2'} is a radical selected from the group consisting of:

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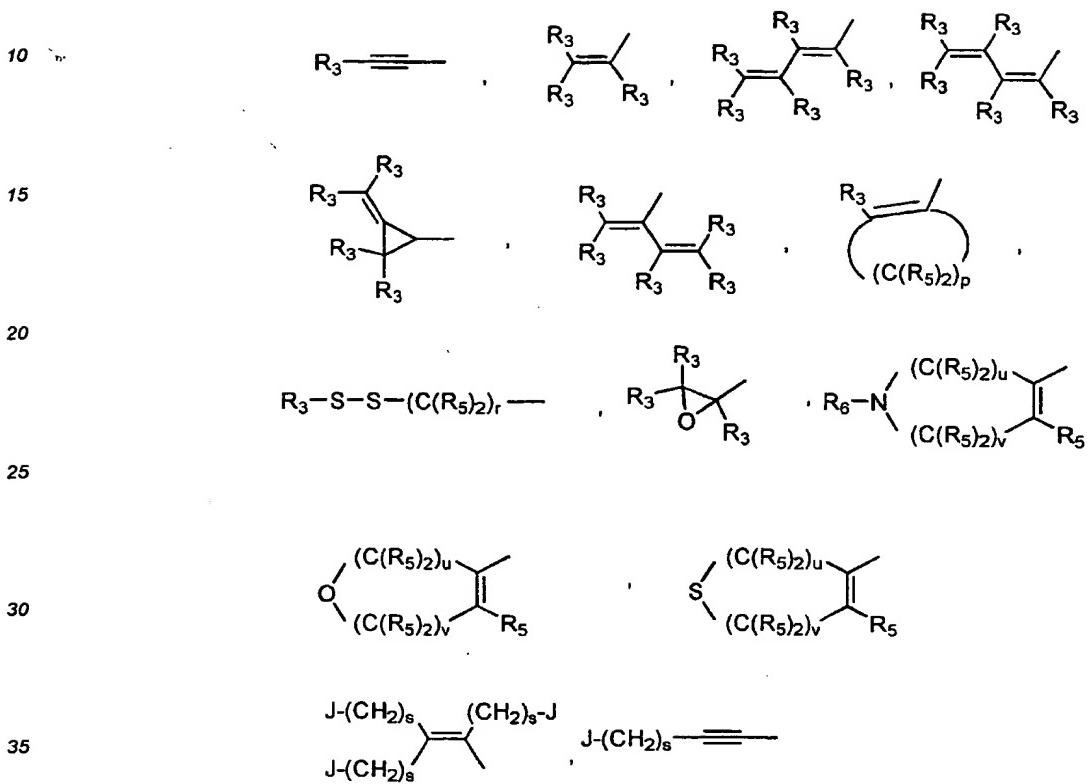
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- 24 -



wherein R₆, R₃, R₅, J, s, r, u, and v are defined. According to the reactions outlined in Flowsheet 4, a 4-chloro-3-cyano-6-nitroquinoline, 16, can be reacted with an amine or aniline 17 by heating in an inert solvent such as tetrahydrofuran, butanol, or methoxyethanol to give compounds of Formula 20 where Z is -NH-. The reaction of 16 with a mercaptan or thiophenol 18 in an inert solvent can be accomplished using a base such as sodium hydride to give compounds of Formula 20 where Z is -S-. The reaction of 16 with a alcohol or phenol 19 in an inert solvent can be accomplished using a base such as sodium hydride to give compounds of Formula 20 where Z is -O-. Compounds of Formula 20 can be reduced to a 6-amino-3-cyano-quinoline, 21, using a reducing agent such as sodium hydrosulfite in a two phase system consisting

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- 25 -

of tetrahydrofuran and water in the presence of a small amount of phase transfer catalyst or by using iron in refluxing protic solvents containing acetic acid or ammonium chloride. Acylation of 21 with either an acid chloride of Formula 22 or a mixed anhydride of Formula 23 (which is prepared from the corresponding carboxylic acid) in an inert solvent such as tetrahydrofuran (THF) in the presence of an organic base such as pyridine, triethylamine, diisopropylethylamine, or N-methyl morpholine gives the compounds of this invention of Formula 24. In those cases where 22 or 23 have an asymmetric carbon atom, they can be used as the racemate or as the individual R or S enantiomers in which case the compounds of this invention will be in the racemic or R and S optically active forms, respectively. In those cases, where the R_{2'} contains primary or secondary amino groups, the amino groups will first have to be protected prior to anhydride or acid chloride formation. Suitable protecting groups include, but are not limited to, tert-butoxycarbonyl (BOC) and benzyloxycarbonyl (CBZ) protecting groups. The former protecting group can be removed from the final products of Formula 24 by treatment with an acid such as trifluoroacetic acid while the latter protecting group can be removed by catalytic hydrogenation. In those cases where the R_{2'} contains hydroxyl groups, the hydroxyl groups may first have to be protected prior to anhydride or acid chloride formation. Suitable protecting groups include, but are not limited to, t-butyldimethylsilyl, tetrahydropyranyl, or benzyl protecting groups. The first two protecting groups can be removed from the final products of Formula 24 by treatment with an acid such as acetic acid or hydrochloric acid while the latter protecting group can be removed by catalytic hydrogenation. In those cases, in intermediates 17, 18, or 19 where X contains primary or secondary amino groups or hydroxyl groups, it may be necessary to protect these groups prior to the reaction with 16. The same amine or alcohol protecting groups described above can be used and they can be removed from the products 24 as previously described.

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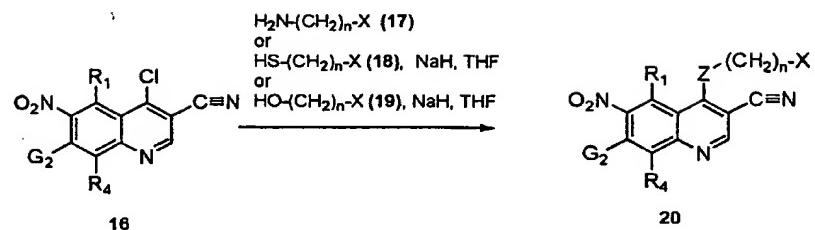
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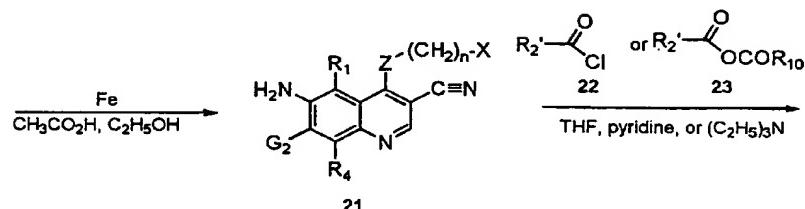
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FLowsheet 4

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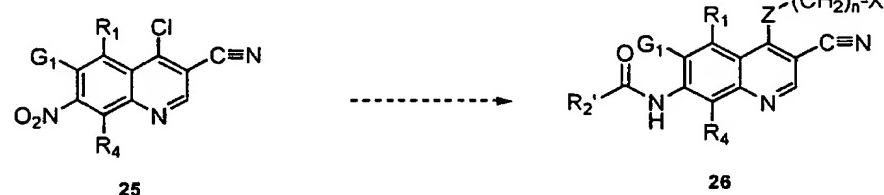


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By using methods similar to that describe above in Flowsheet 4, the intermediates 25
5 can be converted to the compounds of this invention, 26.

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- 27 -

In order to prepare the compounds of this invention, certain amines are required.
10 Some representative amines are shown below in List A wherein R₆, p, and r are as defined above. These amines are available commercially, are known in the chemical literature, or can be prepared by simple procedures that are well known in the art. In
15 5 some cases, these amines may have an asymmetric carbon atoms; they can be used as the racemate or they can be resolved and used as the individual R or S enantiomers in which case the compounds of this invention will be in the racemic or optically active forms, respectively. Throughout this application in the Flowsheets shown below,
20 these amines, and other similar amines, will be represented by the generic structure
10 of the formula:

(R')₂NH , wherein this formula can represent a primary or secondary amine.

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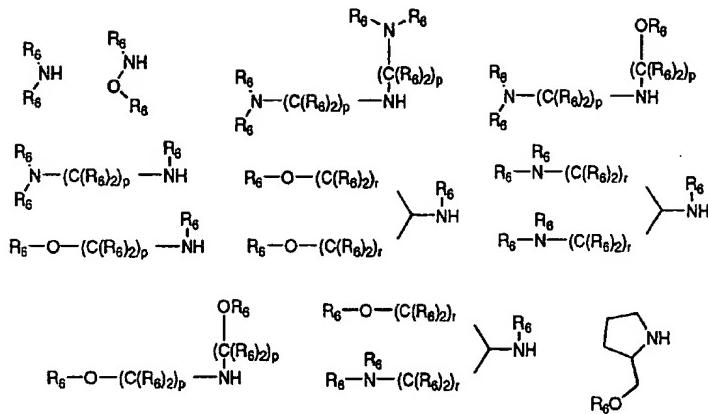
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List A

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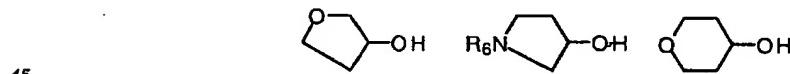
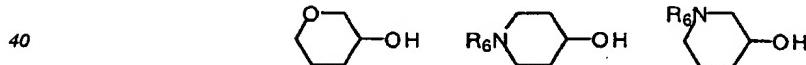
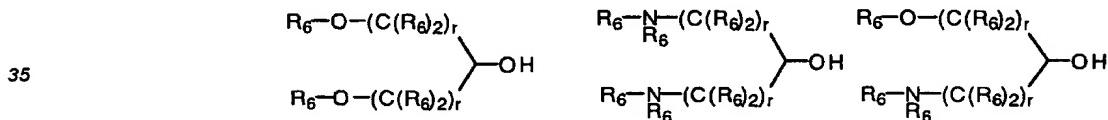
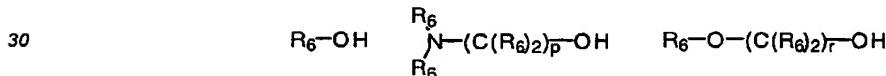
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In order to prepare the compounds of this invention certain alcohols are required. Some representative alcohols are shown below in List B wherein R₆, p, and r are as defined above. These alcohols are available commercially, are known in the chemical literature, or can be prepared by simple procedures that are well known in the art. In some cases, these alcohols may have an asymmetric carbon atoms; they can be used as the racemate or they can be resolved and used as the individual R or S enantiomers in which case the compounds of this invention will be in the racemic or optically active forms, respectively. Throughout this application in the Flowsheets shown below, these alcohols, and other similar alcohols, will be represented by the generic structure of the formula:



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List B



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- 30 -

In order to prepare some of the compounds of this invention certain mixed anhydrides of Formulas 31, 34, and 38 are required; these are prepared as outlined below in Flowsheet 5-6 wherein R₆, R₁₀, X, Z, n, and s are as defined above. J' is a halogen atom chlorine, bromine, or iodine, or is a toslyate (p-toluenesulfonate) or mesylate (methanesulfonate) group. The reaction of 27 with an amine of List A is accomplished by heating in an inert solvent such as tetrahydrofuran or N,N-dimethylformamide, or using potassium or cesium carbonate in acetone. The temperature and duration of the heating will depend on the reactivity of 27; longer reaction times and higher temperatures may be required when s is greater than 1.

10 Treatment of 28 with an alkyl lithium reagent followed by quenching with an atmosphere of dry carbon dioxide furnishes the carboxylic acids of formula 29. These can be converted to mixed anhydrides of Formula 31 using a reagent such as isobutylchloroformate in an inert solvent such as tetrahydrofuran in the presence of a base such as N-methylmorpholine. These anhydrides can then be used to prepare the

15 compounds of this invention as described above in Flowsheet 4. The reaction of 27 with an alcohol of List B is accomplished using sodium hydride or other non-nucleophilic base such as potassium or cesium carbonate in an inert solvent such as tetrahydrofuran, acetone, or N,N-dimethylformamide. In some cases, the alcohol of List B can also be the solvent of the reaction. Treatment of 32 with an alkyl lithium

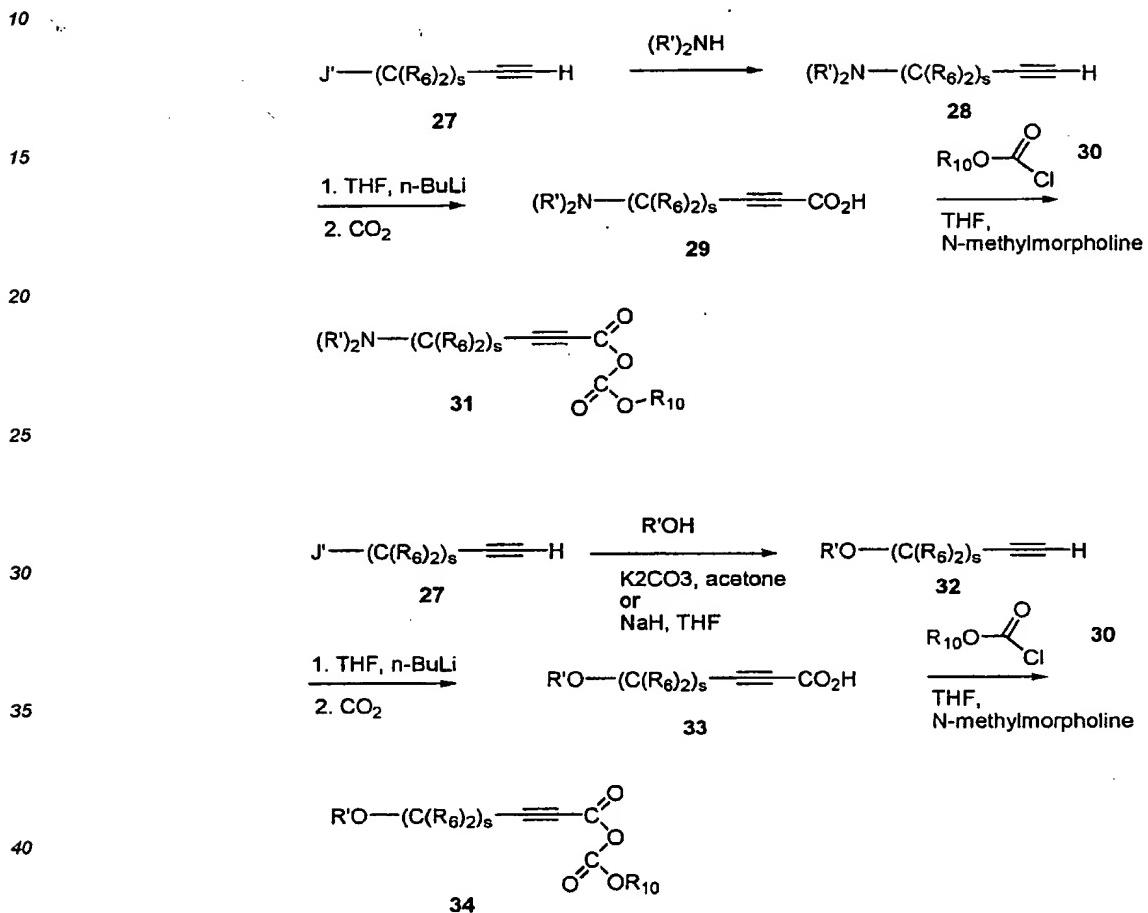
20 reagent followed by quenching with an atmosphere of dry carbon dioxide furnishes the carboxylic acids of formula 33. These can be converted to mixed anhydrides Formula 34 using a reagent such as isobutylchloroformate in an inert solvent such as tetrahydrofuran in the presence of a base such as N-methylmorpholine. These anhydrides can then be used to prepare the compounds of this invention as described

25 above in Flowsheet 4.

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- 31 -

FLOW SHEET 5



As outline in Flowsheet 6 below wherein R₁, G₂, R₄, R₆, R₁₀, X, Z, n, and s are as defined above, alcohols 35 can be protected with a t-butyl dimethylsilyl protecting group by the reaction with the respective silyl chloride in methylene chloride in the presence of triethylamine and 4-N,N-dimethylamino pyridine (DMAP). The resulting protected alcohols, 36, are converted to the acetylenic

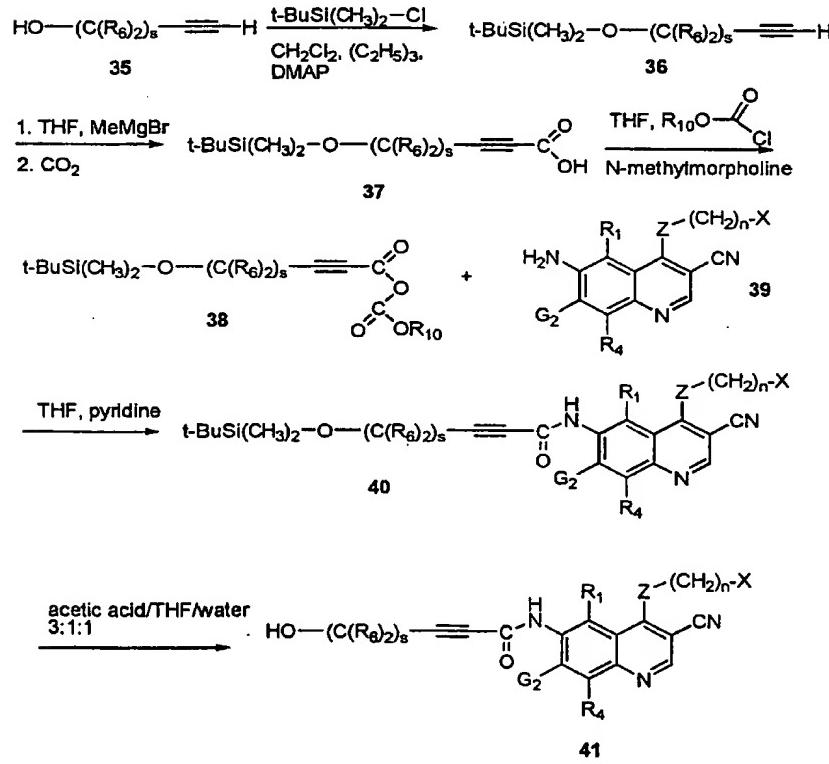
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- 32 -

Grignard reagents which, in turn, are maintained under an atmosphere of dry carbon dioxide to give the carboxylic acids 37. As described above these are converted to the mixed anhydrides 38 which on reaction with the 6-amino3-cyanoquinoline 39 gives 40. In the final step of the sequence, the silyl protecting group is removed by treating 5 with acid in a protic solvent mixture to give the compounds represented by Formula 15
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FLOWSHEET 6

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10 Compounds of this invention are also prepared as shown below in Flowsheet 7
wherein R₁, G₂, R₄, R₆, R₁₀, X, Z, n, and s are as defined above. J' is a halogen
atom chlorine, bromine, or iodine, or is a toslyate or mesylate group. Treatment of 42
15 with an alkyl lithium reagent at low temperature followed by quenching with an
atmosphere of dry carbon dioxide furnishes the carboxylic acids of formula 43. These
can be converted to mixed anhydrides of Formula 44 using a reagent such as
isobutylchloroformate in an inert solvent such as tetrahydrofuran in the presence of a
20 base such as N-methylmorpholine. These anhydrides can then be used to prepare the
compounds of this invention as by the reaction with the 6-amino-3-cyanoquinolines
25 45 described above in the Flowsheets. The reaction of 46 with an alcohol of List B is
accomplished using sodium hydride or other non-nucleophilic base in an inert solvent
such as tetrahydrofuran or N,N-dimethylformamide to give the compounds of this
invention represented by 47. In some cases, the alcohol of List B can also be the
30 solvent of the reaction. The reaction of 46 with an amine of List A gives the
compounds of this invention represented by 48 is accomplished by heating in an inert
solvent such as tetrahydrofuran or N,N-dimethylformamide, or using potassium or
cesium carbonate in acetone. The temperature and duration of the heating will depend
35 on the reactivity of 46; longer reaction times and higher temperatures may be required
when s is greater than 1.

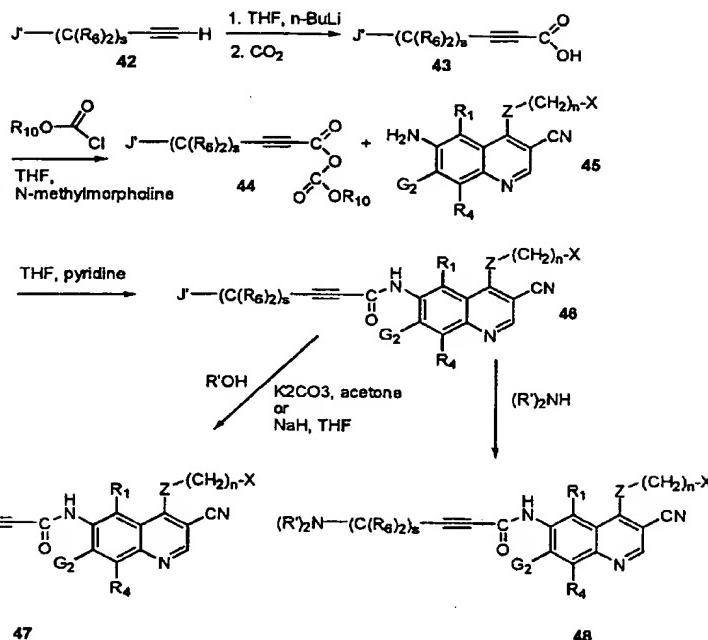
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- 34 -

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FLOWSHEET 7

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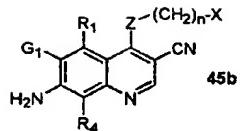
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Using methods similar to that summarized above, 45b can be converted to 47b or
 5 48b.

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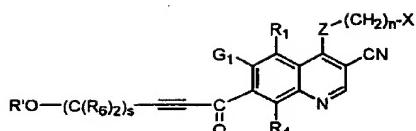
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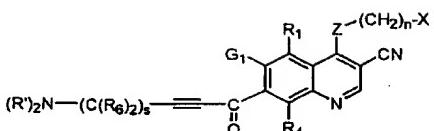


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Other carboxylic acid chlorides and anhydrides needed to prepare some of the compounds of this invention are prepared as shown below in Flowsheet 8 wherein

- 30 5 R₆, R₃, R₁₀, X, Z, J', n, and s are as defined above. Q' is an alkyl group of 1-6 carbon atoms. The esters 49, 53, or 57 can be hydrolyzed with a base such as barium hydroxide to give the respective carboxylic acid 50, 54, or 58. These acid can be converted to the respective carboxylic acid chlorides 51 or 56 by using oxalyl chloride and catalytic N,N-dimethylformamide in an inert solvent or respective mixed
- 35 10 anhydrides 55 or 59 by using isobutyl chloroformate and an organic base such as N-methylmorpholine. The leaving group in compounds represented by Formula 52 can be displaced by the amines of List A or the alcohols of List B by using procedures previously described to give the intermediates 57 and 53, respectively. These carboxylic acid chlorides 51 and 56 and these anhydrides 55 and 59 can be used to
- 40 45 15 prepare some of the compounds of this invention by using the methods outlined herein above in the Flowsheets.

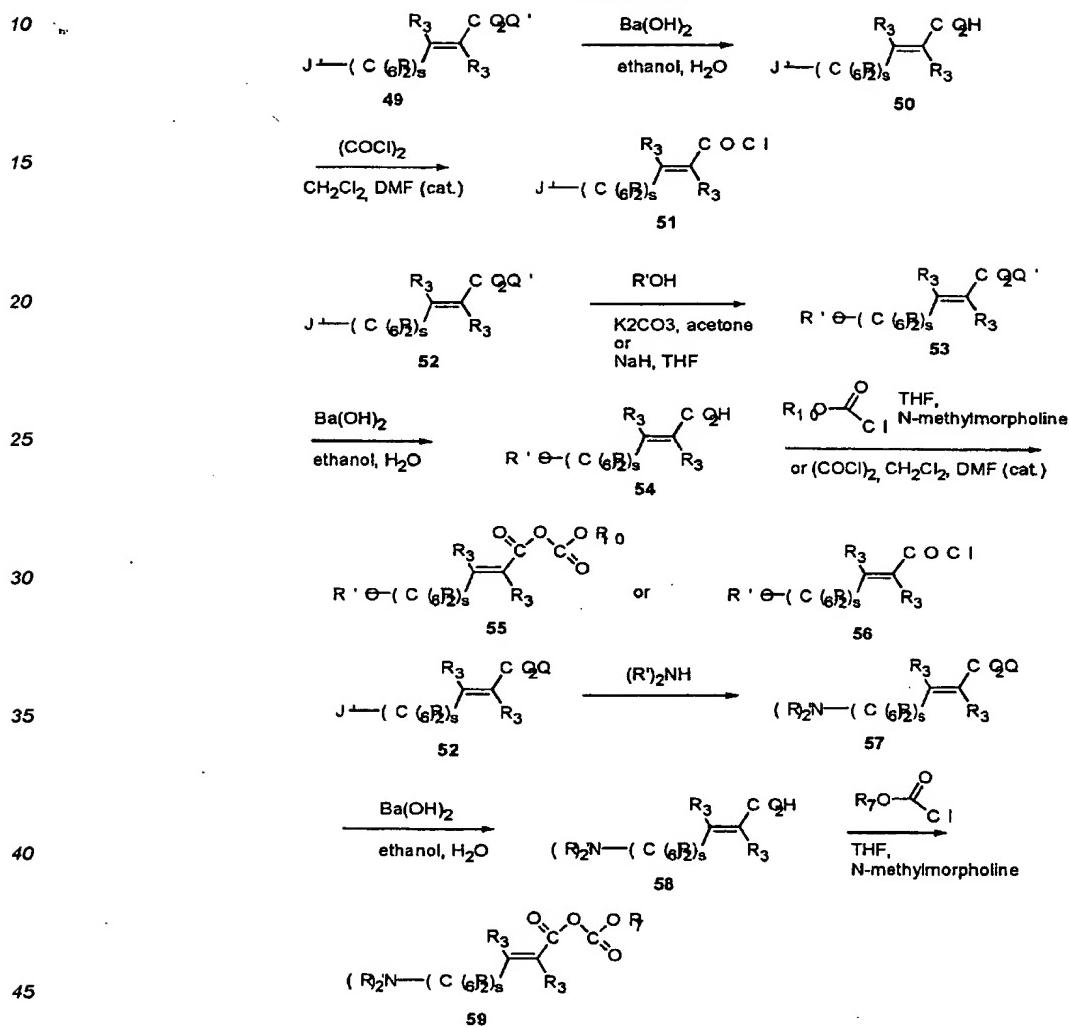
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- 36 -

FLowsheet 8



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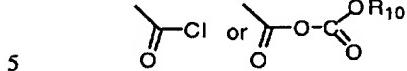
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- 37 -

10 By using the methods identical to those outlined above in Flowsheet 8, it is possible to prepare the analogous carboxylic acid chlorides and anhydrides given below in List C wherein R₆, R₃, p, and s are as previously defined. G is the radical:

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and A is the radical:

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wherein $-\text{N}(\text{R}')_2$ is derived from the amines of List A, $-\text{OR}'$ are derived from the alcohols of List B, and J' is a leaving group as defined previously. By making use of these carboxylic acid chlorides and anhydrides, by following the methods summarized in the above in Flowsheets, and by pursuing the details described in the examples given below, many of the compounds of this invention can be prepared.

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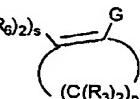
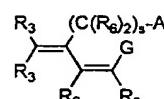
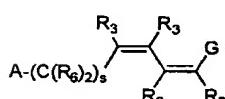
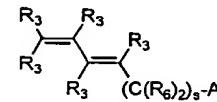
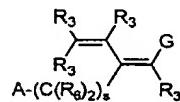
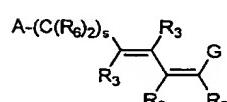
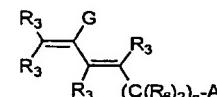
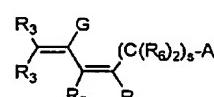
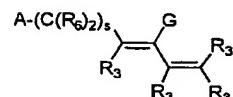
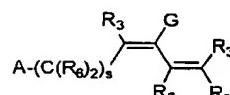
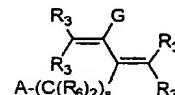
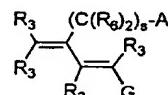
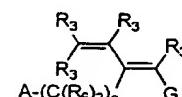
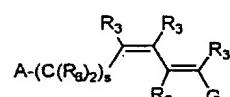
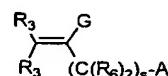
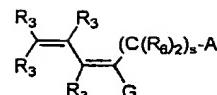
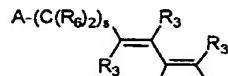
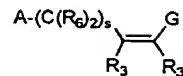
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- 38 -

LIST C

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Compounds of this invention represented by Formulas 62-63 can be prepared as shown in Flowsheet 9 wherein R₁, G₂, R₄, R₆, R₃, R₁₀, X, Z, J', n, and s are as

- 45 defined above. The reaction of the carboxylic acid chlorides 60 and the 6-amino-3-cyanoquinolines 61 using an organic base in an inert solvent gives the compounds of this invention represented by Formula 62. The reaction of 62 with an alcohol of List B is accomplished using sodium hydride or other non-nucleophilic base such as potassium or cesium carbonate in an inert solvent such as tetrahydrofuran, acetone, or
- 50 10 N,N-dimethylformamide to give the compounds of this invention represented by 63.

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- 39 -

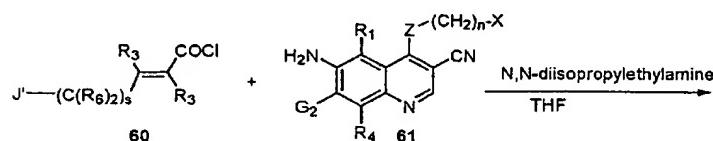
In some cases, the alcohol of List B can also be the solvent of the reaction. The reaction of **62** with an amine of List A to give the compounds of this invention represented by **64** is accomplished by heating in an inert solvent such as tetrahydrofuran or N,N-dimethylformamide. The temperature and duration of the

heating will depend on the reactivity of **62**; longer reaction times and higher temperatures may be required when *s* is greater than 1. In addition, by using this method, the carboxylic acid chlorides and mixed anhydrides listed in List C can be used to prepare the analogous compounds of this invention.

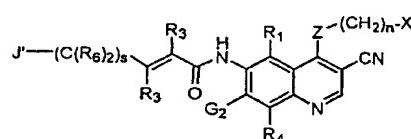
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FLOWSHEET 9

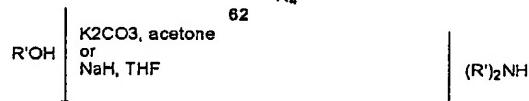
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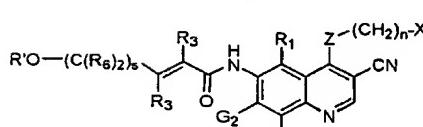
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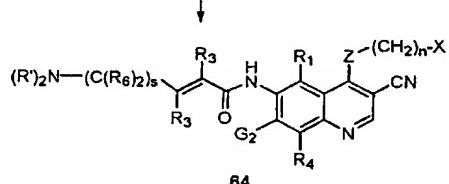
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63**64**

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10 By applying the methods summarized above, **61b** can be converted to **63b** and **64b**
via the intermediate **62b**.

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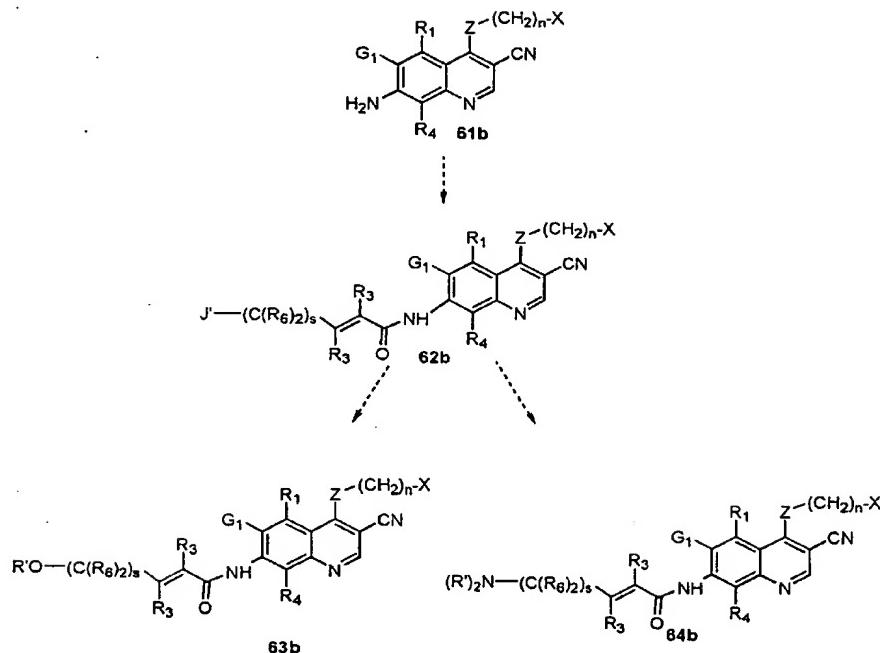
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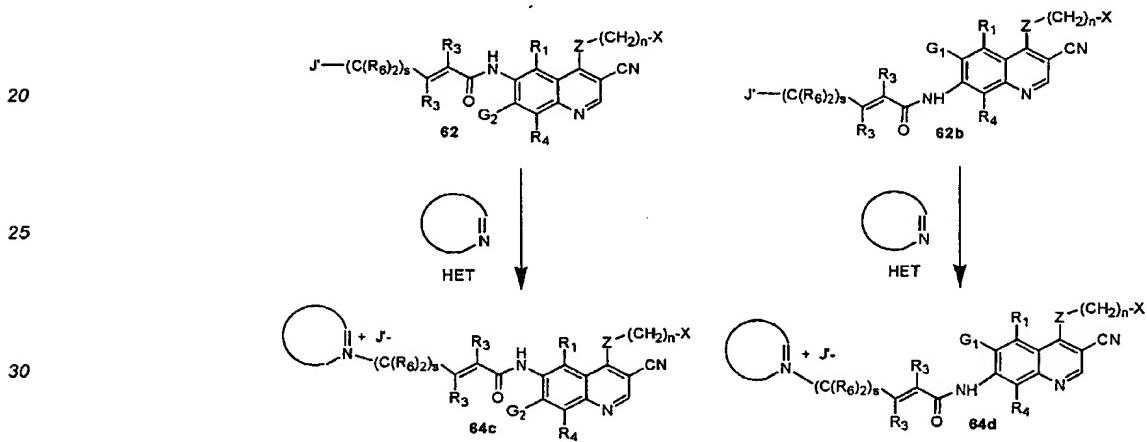
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- 41 -

The reaction of 62 or 62b with a nitrogen containing heterocycle HET which also contains an unsaturated carbon-nitrogen bond is accomplished by refluxing in an inert solvent and gives the compounds of this invention 64c and 64d, respectively where the compound bears a positive charge. The counter anion J'- can be replaced with any other pharmaceutically acceptable anion using the appropriate ion exchange resin.



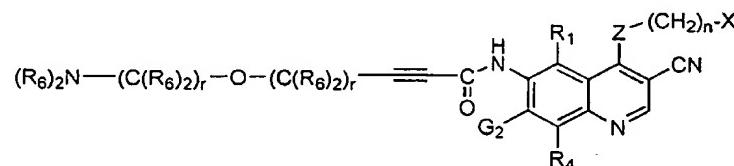
Some of the compounds of this invention can be prepared as outline below in Flowsheet 10 wherein R₁, G₂, R₃, R₄, R₆, R₁₀, X, Z, J', n, and r are as defined above. The acetylenic alcohols 65 can be coupled to the halides, mesylates, or tosylates 66 using a base such as sodium hydride in an inert solvent such as tetrahydrofuran. The resulting acetylene, 67, is then treated with an alkyl lithium reagent at low temperature. Maintaining the reaction under an atmosphere of carbon dioxide then gives the carboxylic acids 68. These, in turn, are reacted with the 6-amino-3-cyanoquinolines, 69, via the mixed anhydrides to give the compounds of this invention represented by Formula 70. Alternatively, the intermediates 67 can be prepared starting with an alcohol 71 by first treating it with a base such as sodium hydride in an inert solvent such as tetrahydrofuran and then adding an acetylene 72 that has an appropriate leaving group. In a similar manner, the amino alcohols

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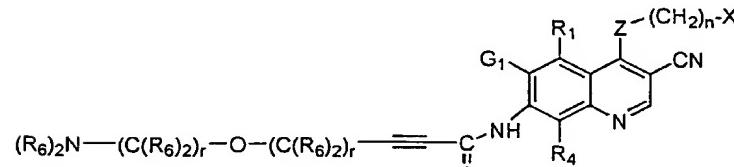
- 42 -

10 represented by the formula: $(R_6)_2N—(C(R_6)_2)_r—OH$ by reacting with 72, and applying the chemistry of Flowsheet 10, can be converted to the compounds of this invention represented by the formulas:

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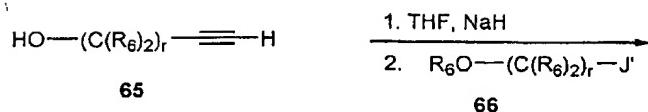
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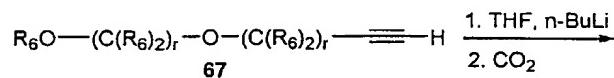
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FLOWSHEET 10

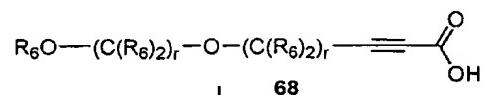
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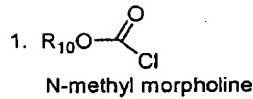
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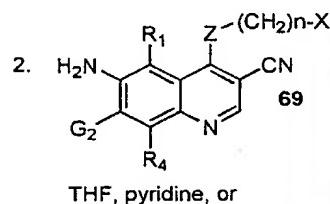
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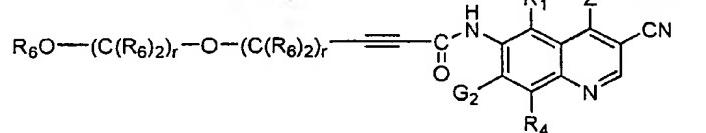
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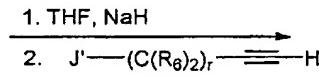
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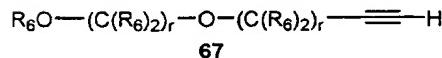
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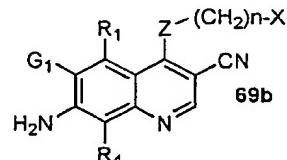
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- 44 -

10 By applying similar methods as described above, 69b can be converted to the compounds of this invention represented by 70b.

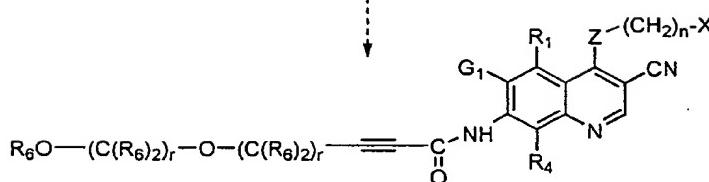
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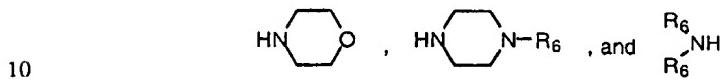
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The compounds of this invention represented by Formula 76 and 77 are prepared as shown below in Flowsheet 11 wherein R1, R3, R4, R6, and n defined above and the amines $\text{HN}(\text{R''})_2$ are selected from the group:

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Refluxing 73 and 74 in an a solvent such as ethanol gives the intermediate 75 which can react with an amine in refluxing ethanol to give the compounds of this invention represented by Formula 76. Treating 75 with an excess of a sodium alkoxide in an

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15 inert solvent or a solvent from which the alkoxide is derived gives the compounds of this invention of Formula 77.

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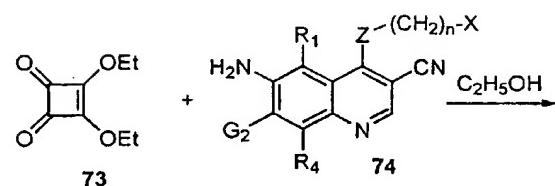
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- 45 -

FLOWSHEET 11

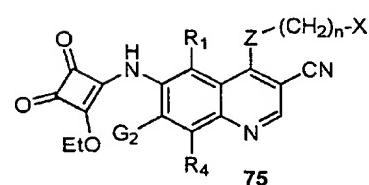
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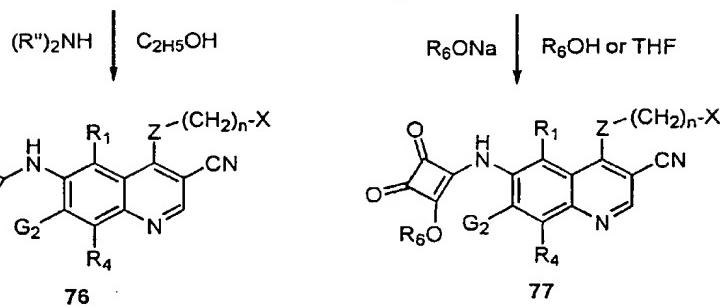
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In a manner similar to that described above, 74b can be converted to 76b or 77b.

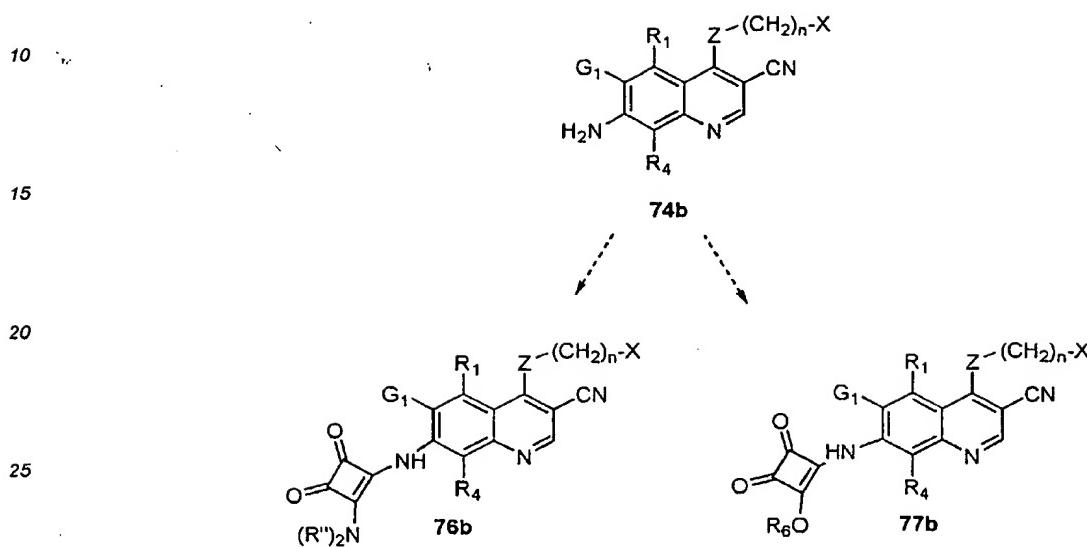
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- 46 -



Compounds of this invention represented by Formula 83 can be prepared as shown in Flowsheet 12 wherein R₁, G₂, R₄, R₆, R₃, R₁₀, X, Z, n, and r are as defined above. The reaction of the mercapto carboxylic acids 78 with the reagents 79 give the compounds represented by Formula 80. Alternatively, 80 can be prepared from the mercaptan R₃SH using the mercapto acid 78, triethylamine and 2,2'-dipyridyl disulfide. Mixed anhydride formation to give 81 followed by condensation with the 6-amino-3-cyanoquinolines 82 give the compounds of this invention.

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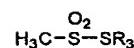
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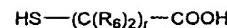
FLOWSHEET 12

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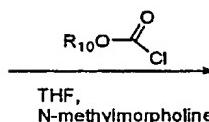


or
2,2'-dipyridyl disulfide, R₃SH
Et₃N, THF

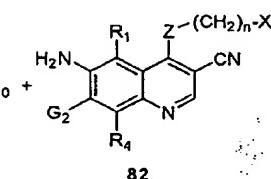


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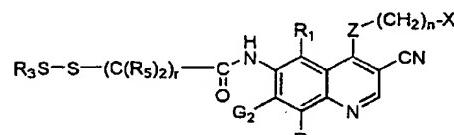
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THF, pyridine



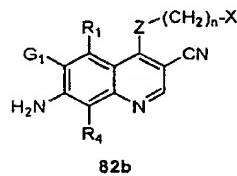
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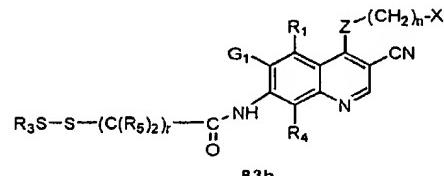
5 By applying similar methods as described above 82b can be converted to 83b.

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83b

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- 48 -

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Compounds of this invention represented by Formulas 86-88 can be prepared as shown in Flowsheet 13 wherein R₁, G₂, R₁, R₄, R₅, J', X, Z, and n are as defined above. Q' is alkyl of 1-6 hydrogen atoms, alkoxy of 1-6 hydrogen atoms, hydroxy, or hydrogen. Akylation of 84 with the 6-amino-3-cyanoquinolines 85 can be accomplished by heating in an inert solvent such as N,N-dimethylformamide using a base such as potassium carbonate to give the compounds of this invention represented by the Formula 86. When Q' is alkoxy, the ester group can be hydrolyzed to an acid using a base such as sodium hydroxide in methanol. In a similar manner, by using intermediates 89 and 90, the compounds of this invention represented by Formulas 87 and 88 can be prepared, respectively.

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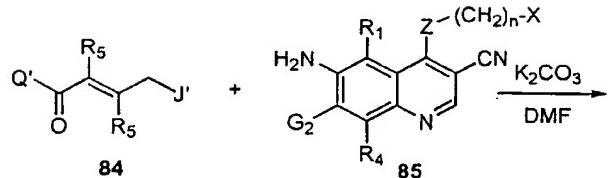
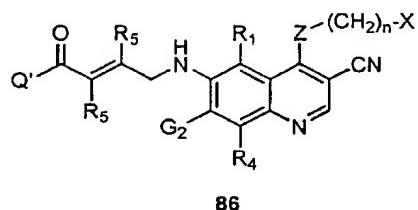
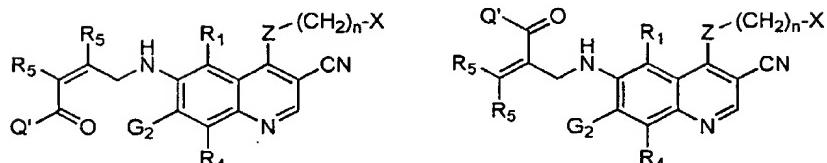
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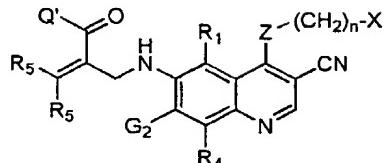
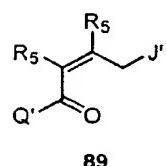
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FLOWSHEET 13

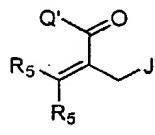
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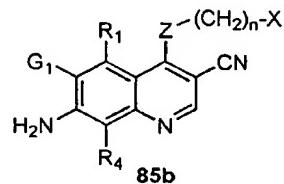
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- 50 -

By applying similar methods as described above 85b can be converted to 86b-88b.

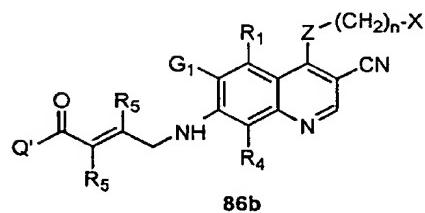
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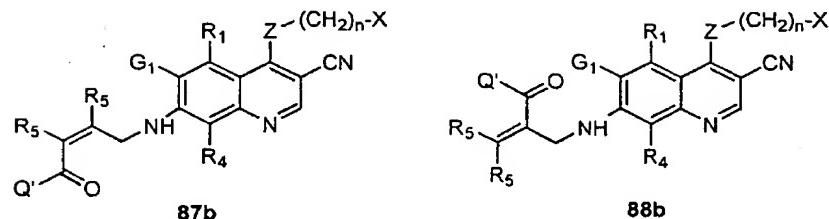
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Compounds of this invention represented by Formula 93 can be prepared as shown in Flowsheet 14 wherein R₁, G₂, R₁, R₄, R₅, X, Z, and n are as defined above. The reaction of reagent 91 with the 6-amino-3-cyanoquinolines 92 is accomplished using an excess of an organic base such as triethylamine and an inert solvent such as tetrahydrofuran to give compounds of this invention represented by Formula 93.

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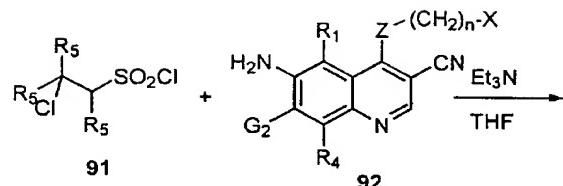
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FLOWSHEET 14

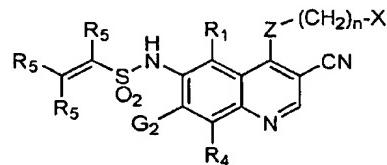
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Compounds of this invention represented by Formula 96 can be prepared as shown in Flowsheet 15 wherein R₁, G₁, R₁, R₄, R₅, R₆, W, Het, X, Z, k, and n are as defined above by the Mitsunobu reaction of phenol 94 and an alcohol 95 in an inert solvent. Alternatively, the Mitsunobu reaction can be applied to compound 97 to give 98. This compound can be converted to 96 as described above in Flowsheet 4. The heterocycle can be introduced at the 6-position by using the corresponding compounds where G₁ is hydroxy and G₂ is located at the 7-position.

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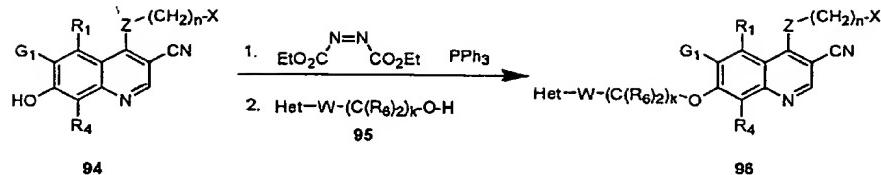
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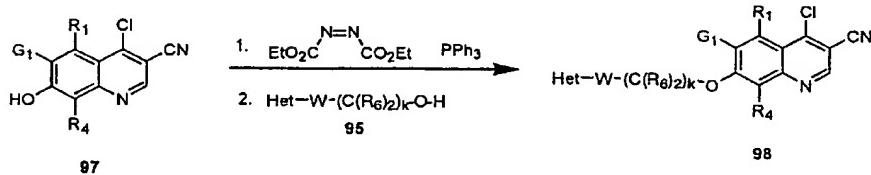
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FLOWSHEET 15

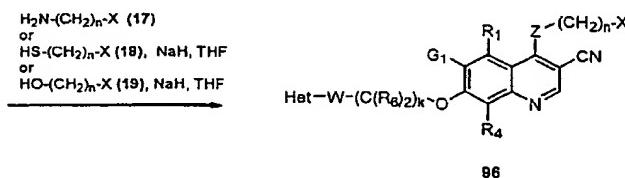
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There are certain functional group manipulations that are useful to prepare the

5 compounds of this invention that can be applied to various intermediate 3-cyanoquinolines as well as to the final compounds of this invention. These manipulations refer to the substituents R₁, G₁, G₂, or R₄ that are located on the 3-cyanoquinolines shown in the above Flowsheets. Some of these functional group manipulations are described below:

45 10 Where one or more of R₁, G₁, G₂, or R₄ is a nitro group, it can be converted to the corresponding amino group by reduction using a reducing agent such as iron in acetic acid or by catalytic hydrogenation. Where one or more of R₁, G₁, G₂, or R₄ is 50 an amino group, it can be converted to the corresponding dialkyamino group of 2 to 12 carbon atoms by alkylation with at least two equivalents of an alkyl halide of 1 to

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- 10 6 carbon atoms by heating in an inert solvent or by reductive alkylation using an
aldehyde of 1 to 6 carbon atoms and a reducing agent such as sodium
cyanoborohydride. Where one or more of R₁, G₁, G₂, or R₄ is a methoxy group, it
can be converted to the corresponding hydroxy group by reaction with a
15 demethylating agent such as boron tribromide in an inert solvent or by heating with
pyridinium chloride with or without solvent. Where one or more of R₁, G₁, G₂, or
R₄ is an amino group, it can be converted to the corresponding alkylsulfonamido,
20 alkenylsulfonamido, or alkynylsulfonamido group of 2 to 6 carbon atoms by the
reaction with an alkylsulfonyl chloride, alkenylsulfonyl chloride, or alkynylsulfonyl
chloride, respectively, in an inert solvent using a basic catalyst such as triethylamine
25 or pyridine. Where one or more of R₁, G₁, G₂, or R₄ is an amino group, it can be
converted to the corresponding alkyamino group of 1 to 6 carbon atoms by alkylation
with one equivalent of an alkyl halide of 1 to 6 carbon atoms by heating in an inert
solvent or by reductive alkylation using an aldehyde of 1 to 6 carbon atoms and a
30 reducing agent such as sodium cyanoborohydride in a protic solvent such as water or
alcohol, or mixtures thereof. Where one or more of R₁, G₁, G₂, or R₄ is hydroxy, it
can be converted to the corresponding alkenyloxy, group of 1-6 carbon atoms by
reaction with an appropriate carboxylic acid chloride, anhydride, or mixed anhydride
35 in a inert solvent using pyridine or a trialkylamine as a catalyst. Where one or more of
R₁, G₁, G₂, or R₄ is hydroxy, it can be converted to the corresponding alkynyoxy group of 1-6 carbon atoms by reaction with an
appropriate carboxylic acid chloride, anhydride, or mixed anhydride in an inert solvent
40 using pyridine or a trialkylamine as a catalyst. Where one or more of R₁, G₁, G₂, or R₄ is hydroxy, it can be converted to
the corresponding alkynyoxy group of 1-6 carbon atoms by reaction with an
appropriate carboxylic acid chloride, anhydride, or mixed anhydride in a inert solvent
45 using pyridine or a trialkylamine as a catalyst. Where one or more of R₁, G₁, G₂, or
R₄ is carboxy or a carboalkoxy group of 2-7 carbon atoms, it can be converted to the
corresponding hydroxymethyl group by reduction with an appropriate reducing agent
50 such as borane, lithium borohydride, or lithium aluminum hydride in a inert solvent;
30 the hydroxymethyl group, in turn, can be converted to the corresponding halomethyl

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group by reaction in an inert solvent with a halogenating reagent such as phosphorous tribromide to give a bromomethyl group, or phosphorous pentachloride to give a chloromethyl group. The hydroxymethyl group can be acylated with an appropriate acid chloride, anhydride, or mixed anhydride in an inert solvent using pyridine or a trialkylamine as a catalyst to give the compounds of this invention with the corresponding alkanoyloxymethyl group of 2-7 carbon atoms, alkenoyloxymethyl group of 2-7 carbon atoms, or alkynoyloxymethyl group of 2-7 carbon atoms. Where one or more of R₁, G₁, G₂, or R₄ is a halomethyl group, it can be converted to an alkoxyloxymethyl group of 2-7 carbon atoms by displacing the halogen atom with a sodium alkoxide in an inert solvent. Where one or more of R₁, G₁, G₂, or R₄ is a halomethyl group, it can be converted to an aminomethyl group, N-alkylaminomethyl group of 2-7 carbon atoms or N,N-dialkylaminomethyl group of 3-14 carbon atoms by displacing the halogen atom with ammonia, a primary, or secondary amine, respectively, in an inert solvent.

In addition to the methods described herein above, there are a number of patent applications that describe methods that are useful for the preparation of the compounds of this invention. Although these methods describe the preparation of certain quinazolines, they are also applicable to the preparation of correspondingly substituted 3-cyanoquinolines. The chemical procedures described in the application WO-9633981 can be used to prepare the 3-cyanoquinoline intermediates used in this invention wherein R₁, G₁, G₂, or R₄ are alkoxyalkylamino groups. The chemical procedures described in the application WO-9633980 can be used to prepare the 3-cyanoquinoline intermediates used in this invention wherein R₁, G₁, G₂, or R₄ are aminoalkylalkoxy groups. The chemical procedures described in the application WO-9633979 can be used to prepare the 3-cyanoquinoline intermediates used in this invention wherein R₁, G₁, G₂, or R₄ are alkoxyalkylamino groups. The chemical procedures described in the application WO-9633978 can be used to prepare the 3-cyanoquinoline intermediates used in this invention wherein R₁, G₁, G₂, or R₄ are aminoalkylamino groups. The chemical procedures described in the application WO-9633977 can be used to prepare the 3-cyanoquinoline intermediates used in this

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invention wherein R₁, G₁, G₂, or R₄ are aminoalkylalkoxy groups. Although the above patent applications describe compounds where the indicated functional group have been introduced onto the 6-position of a quinazoline, the same chemistry can be used to introduce the same groups unto positions occupied by the R₁, G₁, G₂, and R₄

15 substituents of the compounds of this invention

Representative compounds of this invention were evaluated in several standard pharmacological test procedures that showed that the compounds of this invention possess significant activity as inhibitors of protein tyrosine kinases, and are antiproliferative agents. Based on the activity shown in the standard pharmacological 20 test procedures, the compounds of this invention are therefore useful as antineoplastic agents. The test procedures used and results obtained are shown below.

Inhibition of Epidermal Growth Factor Receptor Kinase (EGF-R)

15 using recombinant enzyme

30 Representative test compounds were evaluated for their ability to inhibit the phosphorylation of the tyrosine residue of a peptide substrate catalyzed by the enzyme epidermal growth factor receptor kinase. The peptide substrate (RR-SRC) has the sequence arg-arg-leu-ile-glu-asn-ala-glu-tyr-ala-ala-arg-gly. The enzyme used

35 20 in this assay is the His-tagged cytoplasmic domain of EGFR. A recombinant baculovirus (vHcEGFR52) was constructed containing the EGFR cDNA encoding amino acids 645 - 1186 preceded by Met-Ala-(His)₆. SF9 cells in 100 mm plates were infected at an moi of 10 pfu/cell and cells were harvested 48 h post infection. A 40 cytoplasmic extract was prepared using 1% Triton X-100 and applied to Ni-NTA 25 column. After washing the column with 20 mM imidazole, HcEGFR was eluted with 250 mM imidazole (in 50 mM Na₂HPO₄, pH 8.0, 300 mM NaCl). Fractions collected were dialyzed against 10 mM HEPES, pH 7.0. 50 mM NaCl, 10% glycerol, 45 1ug/mL antipain and leupeptin and 0.1 mM Pefabloc SC. The protein was frozen in dry ice/methanol and stored -70°C.

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Test compounds were made into 10 mg/mL stock solutions in 100% dimethylsulfoxide (DMSO). Prior to experiment, stock solutions were diluted to 500 uM with 100% DMSO and then serially diluted to the desired concentration with HEPES buffer (30 mM HEPES pH 7.4).

For the enzyme reaction, 10 uL of each inhibitor (at various concentrations) were added to each well of a 96-well plate. To this was added 3 uL of enzyme (1:10 dilution in 10mM HEPES, pH 7.4 for final conc. of 1:120). This was allowed to sit for 10 min on ice and was followed by the addition of 5 uL peptide (80 uM final conc.), 10 uL of 4X Buffer (Table A), 0.25 uL ³²P-ATP and 12 uL H₂O. The reaction was allowed to run for 90 min at room temperature and was followed by spotting the entire volume on to precut P81 filter papers. The filter discs were washed 2X with 0.5% phosphoric acid and radioactivity was measured using a liquid scintillation counter.

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Table A

	<u>Reagent</u>	<u>Final</u>	<u>100 Rxns</u>
	1 M HEPES (pH 7.4)	12.5 mM	50 uL
	10mM Na ₃ VO ₄	50 uM	20 uL
	1M MnCl ₂	10 mM	40 uL
	1mM ATP	20 uM	80 uL
	³² P-ATP	2.5uCi	25 uL

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10 The inhibition data for representative compounds of the invention are shown
below in TABLE 1. The IC₅₀ is the concentration of test compound needed to reduce
the total amount of phosphorylated substrate by 50%. The % inhibition of the test
compound was determined for at least three different concentrations and the IC₅₀
15 value was evaluated from the dose response curve. The % inhibition was evaluated
with the following formula:

$$\text{% inhibition} = 100 - [\text{CPM(drug)}/\text{CPM(control)}] \times 100$$

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10 where CPM(drug) is in units of counts per minute and is a number expressing the
amount of radiolabeled ATP (³³P) incorporated onto the RR-SRC peptide substrate
25 by the enzyme after 90 minutes at room temperature in the presence of test compound
as measured by liquid scintillation counting. CPM(control) is in units of counts per
minute and was a number expressing the amount of radiolabeled ATP (³³P)
30 15 incorporated into the RR-SRC peptide substrate by the enzyme after 90 minutes at
room temperature in the absence of test compound as measured by liquid scintillation
counting. The CPM values were corrected for the background counts produced by
ATP in the absence of the enzymatic reaction. The IC₅₀ values in TABLE 1 are
35 averages of the individual determinations.

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TABLE 1 (recombinant enzyme)

Inhibition of Epidermal Growth Factor Receptor Kinase

	<u>Compound</u>	<u>IC50</u> <u>(μM)</u>	<u>Number of</u> <u>Tests</u>
	72	0.006	1
	74	0.01	1
	75	0.0004	2
	76	0.01	2
	77	0.006	1
	79	0.00036	3
	82	0.05	1
	93	1.0	1
	95	0.005	1
	96	0.1	1
	108	0.026	2
	106	0.013	2
	107	0.5	1
	109	0.007	2
	89	0.01	1
	115	0.005	1
	91	0.015	1
	119	0.00005	1
	103	0.008	2

Inhibition of Epithelial Cell Kinase (ECK)

5 In this standard pharmacological test procedure, a biotinylated peptide substrate is first immobilized on neutravidin-coated microtiter plates. The test drug, the Epithelial Cell Kinase (ECK), Mg⁺⁺, sodium vanadate (a protein tyrosine phosphatase inhibitor), and an appropriate buffer to maintain pH (7.2) are then added

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to the immobilized substrate-containing microtiter wells. ATP is then added to initiate phosphorylation. After incubation, the assay plates are washed with a suitable buffer leaving behind phosphorylated peptide which is exposed to horse radish peroxidase (HRP)-conjugated anti-phosphotyrosine monoclonal antibody. The antibody-treated plates are washed again and the HRP activity in individual wells is quantified as a reflection of degree of substrate phosphorylation. This nonradioactive format was used to identify inhibitors of ECK tyrosine kinase activity where the IC_{50} is the concentration of drug that inhibits substrate phosphorylation by 50%. The results obtained for representative compounds of this invention are listed in TABLE 2.

Multiple entries for a given compound indication it was tested multiple times.

Inhibition of Kinase insert Domain containing Receptor (KDR: the catalytic domain of the VEGF receptor)

In this standard pharmacological test procedure, KDR protein is mixed, in the presence or absence of a inhibitor compound, with a substrate peptide to be phosphorylated (a copolymer of glutamic acid and tyrosine, E:Y :: 4:1) and other cofactors such as Mg^{++} and sodium vanadate (a protein tyrosine phosphatase inhibitor) in an appropriate buffer to maintain pH (7.2). ATP and a radioactive tracer (either P^{32} - or P^{33} - labeled ATP) is then add to initiate phosphorylation. After incubation, the radioactive phosphate associated with the acid-insoluble fraction of the assay mixture is then quantified as reflection of substrate phosphorylation. This radioactive format was used to identify inhibitors of KDR tyrosine kinase activity where the IC_{50} is the concentration of drug that inhibits substrate phosphorylation by 50%. The results obtained for representative compounds of this invention are listed in TABLE 2. Multiple entries for a given compound indication it was tested multiple times.

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Mitogen Activated Protein Kinase (MAPK) Assay

To evaluate inhibitors of the MAP (mitogen activated protein) kinase a two component coupled standard pharmacological test procedure, which measures phosphorylation of a serine/threonine residue in an appropriate sequence in the

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substrate in the presence and absence of a putative inhibitor, was used. Recombinant human MEK 1 (MAPKK) was first used to activate recombinant human ERK2 (MAPK) and the activated MAPK (ERK) was incubated with substrate (MBP peptide or MYC peptide) in the presence of ATP, Mg²⁺ and radiolabeled ³²P ATP. The phosphorylated peptide was captured on a P 81 phosphocellulose filter (paper filter or embedded in microtiter plate) washed and counted by scintillation methods.

The peptide substrates used in the assay are MBP, peptide substrate (APRTPGGRR), or synthetic Myc substrate, (KKFELLPTPPLSPSRR•5 TFA. The recombinant enzymes used were prepared as GST fusion proteins of human ERK 2 and human MEK 1. Inhibitor samples were prepared as 10X stocks in 10% DMSO and an appropriate aliquot was used to deliver either 10 ug/ml for a single point screening dose or 100, 10, 1, and 0.1 uM final concentration for a dose response curve. Final DMSO concentrations were less than or equal to 1%.

The reaction was run as follows in 50 mM Tris kinase buffer, pH 7.4 in a reaction volume of 50 ul. The appropriate volume of kinase buffer and inhibitor sample was added to the tube. Appropriate dilution of enzyme was delivered to give 2-5 ug recombinant MAPK (Erk) per tube. The inhibitor was incubated with MAPK (Erk) for 30 min at 0 deg. C. Recombinant Mek (MAPKK) (0.5-2.5 ug) or fully activated Mek (0.05-0.1 units) was added to activate the Erk and incubated for 30 min at 30° C. Then substrate and gamma ³²P ATP was were added to give a final concentration of 0.5- 1 mM MBPP or 250-500 uM Myc; 0.2-0.5 uCi gamma P 33 ATP/tube; 50 μM ATP final concentration. Samples were incubated at 30°C for 30 minutes and the reaction was stopped by adding 25 μl of ice cold 10 %TCA .After samples were chilled on ice for 30 min, 20 μl of sample was transferred onto P 81 phosphocellulose filter paper or appropriate MTP with embedded P 81 filter. Filter papers or MTP were washed 2 times with a large volume of 1% acetic acid, then 2 times with water. The filters or MTP were briefly air dried before addition of scintillant and samples were counted in the appropriate scintillation counter set up for reading ³²P isotope. Samples included a positive control (activated enzyme plus substrate); a no enzyme control; a no substrate control; samples with different

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concentrations of putative inhibitor; and samples with reference inhibitors (other active compounds or non-specific inhibitors such as staurosporine or K252 B).

The raw data was captured as cpm. Sample replicates were averaged and corrected for background count. Mean cpm data was tabulated by group and % inhibition by a test compound was calculated as (corrected cpm control- corrected cpm sample/control) X 100 = % inhibition. If several concentrations of inhibitor were tested, IC₅₀ values (the concentration which gives 50% inhibition) were determined graphically from the dose response curve for % inhibition or by an appropriate computer program. The results obtained for representative compounds of this invention are listed in TABLE 2 where there may be separate entries for the same compound; this is an indication that the compound was evaluated more than one time.

TABLE 2
Inhibition of Kinase Insert Domain containing Receptor (KDR), Epithelial Cell Kinase (Eck), and Mitogen Activated Protein Kinase (Mek-Erk)

	Example	VEGF μM	Eck μM	Mek and Erk μM	erbB2 % Inh 2 μg/mL
15	72		> 41.724	> 100	96
20	74		> 42.982	> 100	95
	75		> 37.284	100	
	76		> 40.617	> 100	96
35	77		42.162	> 100	105
	78		> 21.269	40	53
40	79		> 38.610	80	
	82	> 1.8315	> 1.832	30	
	85		> 21.584	10	87
				4	
				1.8	
	30			1.8	

Inhibition of Cancer Cell Growth as Measured by Cell Number

Human tumor cell lines were plated in 96-well plates (250 μl/well, 1.6 x 10⁴ cells/ml) in RPMI 1640 medium, containing 5% FBS (Fetal Bovine Serum). Twenty four hours after plating, test compounds were added at five log concentrations (0.01-100 mg/ml) or at lower concentrations for the more potent compounds. After 48 hours exposure to test compounds, cells were fixed with trichloroacetic acid, and

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stained with Sulforhodamine B. After washing with trichloroacetic acid, bound dye
 10 was solubilized in 10 mM Tris base and optical density was determined using plate
 reader. Under conditions of the assay the optical density is proportional to the number
 15 of cells in the well. IC₅₀s (concentrations causing 50% inhibition of cell growth) were
 5 determined from the growth inhibition plots. The test procedure is described in details
 by Philip Skehan et. al, *J.Natl. Canc. Inst.*, 82, 1107-1112 (1990). These data are
 20 shown below in TABLE 3. Information about some of the cell lines used in these
 test procedures is available from the American Type Tissue Collection: Cell Lines
 and Hybridomas, 1994 Reference Guide, 8th Edition.

10

Table 3**Inhibition of Cancer Cell Growth as Measured by Cell Number (IC₅₀ µg/mL)**

25

	<u>Example</u>	<u>MDAMB435</u>	<u>SW620</u>	<u>A431</u>	<u>SKBR3</u>	<u>3T3</u>	<u>Her2/3T3</u>
30	15	85	27.6	17.98	4.91	1.74	
		75	0.2	0.5	0.1	0.04	
		74	3.9	0.6	0.9	1.0	
		72	3.5	0.4	0.9	0.8	
		77	0.1	0.1	0.03	0.02	
	20	79	0.3	0.1	0.04	0.01	
35		76	0.284	0.239	0.050	0.031	
		78	3.194	>5	0.369	1.495	
		91	1.83	1.73	0.232	0.181	2.87
		89	2.07	1.53	0.245	0.107	2.04
	40	25	90	1.74	0.234	0.148	2.1
45		92	3.32	2.51	0.283	0.188	2.79
							0.35

In Vivo Inhibition of the Growth of Human Epidermoid Tumors (A431)

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30 BALB/c nu/nu female mice (Charles River, Wilmington, MA) were used in
 the in vivo standard pharmacological test procedures. Human epidermoid carcinoma
 50 cells A-431 (American Type Culture Collection, Rockville, Maryland # CRL-155)
 were grown in vitro as described above. A unit of 5 X 10⁶ cells were injected SC

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10 into mice. When tumors attained a mass of between 100 and 150 mg, the mice were randomized into treatment groups (day zero). Mice were treated IP or PO once a day either on days 1, 5, and 9 or on days 1 through 10 post staging with doses of either 80, 40 or 20, or 10 mg/kg/dose of the compound to be evaluated in 0.2% Klucel.

15 5 Control animals received no drug. Tumor mass was determined every 7 days [(length X width²)/2] for 28 days post staging. Relative tumor growth (Mean tumor mass on day 7, 14, 21, and 28 divided by the mean tumor mass on day zero) is determined for each treatment group. The %T/C (Tumor/Control) is determined by dividing the relative tumor growth of the treated group by the relative tumor growth of the placebo

20 10 group and multiplying by 100. A compound is considered to be active if the %T/C is found to be significantly less than 100%.

25 The ability of the compound of Example 92 to inhibit the growth of human epidermoid tumors (A431) in vivo demonstrated below in TABLE 4 below.

15

30 TABLE 4
In Vivo Inhibition of the Growth of Human Epidermoid Tumors (A431) in Mice
by the Compound of Example 92

20

a	b	c,d	b	c,d	b	c,d	b	c,d	e
Drug Treatment mg/kg/dose	Day 7	% T/C	Day 14	% T/C	Day 20	% T/C	Day 28	% T/C	S/T
0.5% Methocel 0.4% Tween 80	5.51		10.43		12.36		14.18		10/10
Example 92 (40 PO)	1.49	27*	1.58	15*	2.60	21*	6.22	44	5/5
Example 92 (10 PO)	3.94	72	10.41	100	14.76	119	22.51	159	5/5

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a) compound administered on days 1 through 10 PO.

b) Relative Tumor Growth = $\frac{\text{Mean Tumor Mass on Day 7, 14, 21, 28}}{\text{Mean Tumor Mass on Day 0}}$ c) % T/C = $\frac{\text{Relative Tumor Growth of Treated Group}}{\text{Relative Tumor Growth of Placebo Group}} \times 100$ d) Statistical Analysis (Student's T-test) of Log Relative Tumor Growth. * Indicates statistically ($p < 0.01$) significant reduction in Relative Tumor Growth of Treated Group compared to the Placebo Control.

e) S/T = # of Survivors/# of Treated on Day +28 post tumor staging.

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As indicated by the results presented in TABLE 4, the compound of Example 92 is an effective inhibitor of tumor growth *in vivo* when given orally at 40 mg/Kg.

The ability of the compound of Example 89 to inhibit the growth of human epidermoid tumors (A431) in vivo demonstrated below in TABLE 5 below.

TABLE 5
**In Vivo Inhibition of the Growth of Human Epidermoid Tumors (A431) in Mice
 by the Compound of Example 89**

a	b	c,d	b	c,d	b	c,d	b	c,d	e
Drug Treatment mg/kg/dose	Day 7	% T/C	Day 14	% T/C	Day 21	% T/C	Day 28	% T/C	S/T
0.5% Methocel 0.4% Tween 80	4.18		10.44		15.08		28.23		9/10
Example 89 (40 PO)	0.49	11*	0.58	6*	3.11	21*	7.20	26*	5/5
Example 89 (10 PO)	2.09	50*	3.37	32*	5.76	38*	7.24	26*	4/5

a) compound administered on days 1 through 10 PO.

b) Relative Tumor Growth = Mean Tumor Mass on Day 7, 14, 21, 28

Mean Tumor Mass on Day 0

Relative Tumor Growth of Treated Group

d) Statistical Analysis (Student's T-test) of Log Relative Tumor Growth. * Indicates statistically ($p < 0.01$) significant reduction in Relative Tumor Growth of Treated Group compared to the Placebo

Control. *Control* is a term used to describe the process of monitoring and adjusting a system to ensure it operates as intended. It involves setting goals, establishing performance standards, and taking corrective actions when actual performance deviates from the desired outcome.

As indicated by the results presented in TABLE 5, the compound of Example 89 is an effective inhibitor of tumor growth in vivo when given orally at 40 mg/Kg and 10 mg/Kg .

Based on the results obtained for representative compounds of this invention, the compounds of this invention are antineoplastic agents which are useful in treating, inhibiting the growth of, or eradicating neoplasms. In particular, the compounds of this invention are useful in treating, inhibiting the growth of, or eradicating neoplasms that express EGFR such as those of the breast, kidney, bladder, mouth, larynx, esophagus, stomach, colon, ovary, or lung. In addition, the compounds of this invention are useful in treating, inhibiting the growth of, or eradicating neoplasms of

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the breast that express the receptor protein produced by the erbB2 (Her2) oncogene.
10 Based on the results obtained, the compounds of this invention are also useful in the treatment of polycystic kidney disease.

15 5 The compounds of this invention may be formulated neat or may be combined with one or more pharmaceutically acceptable carriers for administration. For example, solvents, diluents and the like, and may be administered orally in such forms as tablets, capsules, dispersible powders, granules, or suspensions containing, for example, from about 0.05 to 5% of suspending agent, syrups containing, for
20 10 example, from about 10 to 50% of sugar, and elixirs containing, for example, from about 20 to 50% ethanol, and the like, or parenterally in the form of sterile injectable solution or suspension containing from about 0.05 to 5% suspending agent in an isotonic medium. Such pharmaceutical preparations may contain, for example, from about 0.05 up to about 90% of the active ingredient in combination with the carrier,
25 15 more usually between about 5% and 60% by weight.

30 30 The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration and the severity of the condition being treated. However, in general, satisfactory results are obtained when the compounds of the invention are administered at a daily dosage of from about 0.5
35 35 20 to about 1000 mg/kg of body weight, optionally given in divided doses two to four times a day, or in sustained release form. The total daily dosage is projected to be from about 1 to 1000 mg, preferably from about 2 to 500 mg. Dosage forms suitable for internal use comprise from about 0.5 to 1000 mg of the active compound in intimate admixture with a solid or liquid pharmaceutically acceptable carrier. This
40 40 25 dosage regimen may be adjusted to provide the optimal therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

45 45 The compounds of this invention may be administered orally as well as by intravenous, intramuscular, or subcutaneous routes. Solid carriers include starch,
50 50 30 lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid carriers include sterile water; polyethylene glycols, non-ionic surfactants and

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edible oils such as corn, peanut and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvants customarily employed in the preparation of pharmaceutical compositions may be advantageously included, such as flavoring agents, coloring agents, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT and BHA.

The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules. Oral administration of the compounds is preferred.

In some cases it may be desirable to administer the compounds directly to the airways in the form of an aerosol.

The compounds of this invention may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

For the treatment of cancer, the compounds of this invention can be administered in combination with other antitumor substances or with radiation therapy. These other substances or radiation treatments can be given at the same or at different times as the compounds of this invention. These combined therapies may effect synergy and result in improved efficacy. For example, the compounds of this

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invention can be used in combination with mitotic inhibitors such as taxol or
10 vinblastine, alkylating agents such as cisplatin or cyclophosphamide, antimetabolites such as 5-fluorouracil or hydroxyurea, DNA intercalators such as adriamycin or bleomycin, topoisomerase inhibitors such as etoposide or camptothecin,
15 antiangiogenic agents such as angiostatin, and antiestrogens such as tamoxifen.

The preparation of representative examples of the compounds of this invention is described below.

Example 1

10 1,4-Dihydro-7-methoxy-4-oxo-quinoline-3-carbonitrile

A mixture of 30.2 g (245.2 mmol) of 3-methoxy aniline and 41.5 g (245.2 mmol) of ethyl(ethoxymethylene) cyanoacetate was heated in the absence of solvent to 140°C for 30 minutes. To the resulting oil was added 1200 ml of Dowtherm. The solution was refluxed with stirring under nitrogen for 22 hours. The mixture was cooled to room temperature and solid was collected and washed with hexanes. The solid was recrystallized from acetic acid to give 17 g of 1,4-dihydro-7-methoxy-4-oxo-quinoline-3-carbonitrile: mass spectrum (electrospray, m/e): M+H 200.9.

Example 2

35 1,4-Dihydro-7-methoxy-6-nitro-4-oxo-quinoline-3-carbonitrile

To a suspension of 10 g (49.6 mmol) of 1,4-dihydro-7-methoxy-4-oxo-quinoline-3-carbonitrile in 160 ml of trifluoroacetic anhydride was added 6 g (74.9 mmol) of ammonium nitrate over a period of 3 hours. The mixture was stirred an additional two hours. Excess anhydride was removed at reduced pressure at 45°C. The residue was stirred with 500 ml of water. The solid was collected and washed with water. The solid was dissolved in 1000 ml of boiling acetic acid and the solution was treated with decolorizing charcoal. The mixture was filtered and concentrated to a volume of 300 ml. Cooling gave a solid which was collected giving 5.4 g of 1,4-dihydro-7-methoxy-6-nitro-4-oxo-quinoline-3-carbonitrile as a brown solid: mass spectrum (electrospray, 40 m/e): M+H 246.

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Example 3

10 4-Chloro-7-methoxy-6-nitro-quinoline-3-carbonitrile

A mixture of 5.3 g (21.6 mmol) of 1,4-dihydro-7-methoxy-6-nitro-4-oxo-quinoline-3-carbonitrile and 9 g (43.2 mmol) of phosphorous pentachloride was heated at 5 165°C for 2 hours. The mixture was diluted with hexanes and the solid was collected. The solid was dissolved in 700 ml ethyl acetate and washed with cold dilute sodium hydroxide solution. The solution was dried over magnesium sulfate and filtered through a pad of silica gel giving 5.2 g of 4-chloro-7-methoxy-6-nitro-quinoline-3-carbonitrile as a tan solid.

10

Example 4

25 4-[(3-Bromophenyl)amino]-7-methoxy-6-nitro-quinoline-3-carbonitrile

A solution of 5.2 g (19.7 mmol) of 4-chloro-7-methoxy-6-nitro-quinoline-3-carbonitrile and 3.7 g (21.7 mmol) of 3-bromo aniline in 130 ml of methoxyethanol 15 was refluxed under nitrogen for 4 hours. The reaction mixture was poured into dilute sodium bicarbonate solution. Solid was collected and washed with water and dried in air. The solid was chromatographed on silica gel eluting with chloroform-ethyl acetate 9:1. Solvent was removed from product fractions giving 1.2 g of 4-[(3-bromophenyl)amino]-7-methoxy-6-nitro-quinoline-3-carbonitrile as a yellow solid:

35 20 mass spectrum (electrospray, m/e): M+H 399.0, 402.0.

Example 5

40 6-Amino-4-[(3-bromophenyl)amino]-7-methoxy-quinoline-3-carbonitrile

A mixture of 2.05 g (5.1 mmol) of 4-[(3-bromophenyl)amino]-7-methoxy-6-nitro-25 quinoline-3-carbonitrile, 1.37 g (25.7 mmol) of ammonium chloride, and 0.86 g (15.4 mmol) of powdered iron was stirred at reflux in 26 ml water and 26 ml methanol for 45 2 hours. The mixture was diluted with ethyl acetate and the hot mixture was filtered. The organic layer was separated from the filtrate and dried over magnesium sulfate. The solvent was removed and the residue was chromatographed on silica gel eluting 30 with mixtures of chloroform and ethyl acetate. Product fractions were combined to

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10 give 1.3 g of 6-amino-4-[(3-bromophenyl)amino]-7-methoxy-quinoline-3-carbonitrile
as a yellow solid: mass spectrum (electrospray, m/e): M+H 369.1, 371.1.

Example 6**2-Cyano-3-(4-nitrophenylamino)acrylic Acid Ethyl Ester**

15 4-Nitroaniline (60.0g, 0.435mol) and ethyl(ethoxymethylene) cyanoacetate (73.5g,
0.435mol) were mixed mechanically in a flask. The mixture was heated at 100°C for
0.5h after it had melted and resolidified. A 114 g portion of the crude product was
20 recrystallized from dimethylformamide to give 44.2g of yellow crystals; mp 227-

10 228.5°C.

Example 7**1,4-Dihydroquinoline-6-Nitro-4-oxo-3-carbonitrile**

25 A slurry of 25.0g (95.8mmol) of 2-cyano-3-(4-nitrophenylamino)acrylic acid ethyl
30 ester in 1.0L of Dowtherm A was heated at 260°C under N₂ for 12.5h. The cooled
reaction was poured into 1.5L of hexane. The product was collected, washed with
hexane and hot ethanol and dried in vacuo. There was obtained 18.7g of brown solid.
An analytical sample was obtained by recrystallization from dimethyl-
35 formamide/ethanol: mass spectrum (electrospray, m/e): M+H 216.

20

Example 8**4-Chloro-6-nitro-quinoline-3-carbonitrile**

40 A mixture of 31.3g (0.147mol) of 6-nitro-4-oxo-1,4-dihydro-quinoline-3-carbonitrile
and 160mL of phosphorous oxychloride was refluxed for 5.5h. The phosphorous
25 oxychloride was removed in vacuo and the residue was poured over ice and
neutralized with sodium bicarbonate. The product was collected, washed with water
45 and dried in vacuo (50°C). There was obtained 33.5g of tan solid; solid: mass
spectrum (electrospray, m/e): M+H 234.

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Example 9

4-[(3-Bromophenyl)amino]-6-nitro-quinoline-3-carbonitrile

A mixture of 17.0g (73.1mmol) of 4-chloro-6-nitro-quinoline-3-carbonitrile and 15.1g (87.7mmol) of 3-bromoaniline in 425mL of ethanol was refluxed for 5h.

5 Saturated sodium bicarbonate was added and then all volatile material was removed in vacuo. The residue was slurried with hexane and the product was collected and washed with hexane. The crude product was washed with water and dried in vacuo(60°C). There was obtained 22.5g of yellow solid. An analytical sample was obtained by recrystallization from ethyl acetate; mp 258-259°C.

10

Example 10

6-Amino-4-[(3-bromophenyl)amino]-quinoline-3-carbonitrile

A mixture of 4.00g (10.8mmol) of 4-[(3-bromophenyl)amino]-6-nitro-quinoline-3-carbonitrile and 12.2g (54.2mmol) of SnCl₂ dihydrate in 160mL of ethanol was

15 refluxed under N₂ for 1.3h. After cooling to 25°C, ice water and sodium bicarbonate were added and the mixture was stirred for 2h. Extraction with chloroform, treatment with Darco, drying (magnesium sulfate) and solvent removal gave 3.9g of brown crystals: mass spectrum (electrospray, m/e): M+H 339.

35

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Example 11

4-[(3,4-Dibromophenyl)amino]-6-nitro-quinoline-3-carbonitrile

A mixture of 6.20g (26.6mmol) of 4-chloro-6-nitro-quinoline-3-carbonitrile and 8.00g (31.9mmol) of 3,4-dibromoaniline in 160mL of ethanol was refluxed under N₂ for 5h. Saturated sodium bicarbonate was added and volatile material was removed. The

25 residue was slurried with hexane, collected, washed with hexane and water and dried. The insoluble material was repeatedly extracted with boiling ethyl acetate and the solution was then filtered through silica gel. The solvent was removed to give 3.80g of green solid: mass spectrum (electrospray, m/e): M+H 449.

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Example 12

10 6-Amino-4-[(3,4-dibromophenyl)amino]-quinoline-3-carbonitrile
A mixture of 4.90g (10.9mmol) of 4-[(3,4-dibromophenyl)amino]-6-nitro-quinoline-
3-carbonitrile and 12.4g (54.7mmol) of SnCl₂ dihydrate in 200mL of ethanol was
15 refluxed under N₂ for 1.5h. After cooling to 25°C, the reaction was diluted with ice
water, neutralized with sodium bicarbonate and stirred for 2h. This solution was then
20 extracted with chloroform, treated with Darco, dried(magnesium sulfate) and
evaporated. After drying in vacuo(40°C), there was obtained 1.25g of brown solid:
mass spectrum (electrospray, m/e): M+H 417, 419, 421.

10

Example 13

25 6-Nitro-4-[(3-trifluoromethylphenyl)amino]-quinoline-3-carbonitrile
A mixture of 10.6g (45.7mmol) of 4-chloro-6-nitro-quinoline-3-carbonitrile and
30 8.82g (54.8mmol) of 3-(trifluoromethyl)aniline in 270 mL of ethanol was refluxed
15 under N₂ for 5h. The reaction was diluted with ethanol, neutralized with said sodium
bicarbonate and evaporated. The residue was slurried with hexane, collected, washed
with hexane and water and dried in vacuo(60°C) to give 10.9g of yellow solid. A
2.00g sample was recrystallized from ethanol to give 1.20g of bright yellow solid; mp
35 260-261°C.

20

Example 14

40 6-Amino-4-[(3-trifluoromethylphenyl)amino]-quinoline-3-carbonitrile
A slurry of 6.00g(16.8mmol) of 6-nitro-4-[(3-trifluoromethylphenyl)amino]-
45 quinoline-3-carbonitrile and 18.9g (83.3mmol) of SnCl₂ dihydrate in 240 mL of
25 ethanol was refluxed under N₂ for 1h. After cooling to 25°C, the reaction was diluted
with ice water, neutralized with sodium bicarbonate and stirred for 2h. The product
was extracted with chloroform, treated with Darco, dried(magnesium sulfate) and
evaporated. The residue was filtered through silica gel(10% methanol in chloroform),
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10 evaporated and dried in *vacuo*(40°C) to give 4.87g of brown solid: mass spectrum (electrospray, m/e): M+H 329.

Example 15

15 5 4-Bromo-but-2-enoic acid [4-(3-bromo-phenylamino)-3-cyano-quinolin-6-yl]-amide.
A solution of 1.65 grams (0.01 mole) of 4-bromo crotonic acid (Giza Braun, J. Am. Chem. Soc. 52, 3167 1930) in 15ml of dichloromethane was treated with 1.74 ml (0.02 moles) of oxalyl chloride and 1 drop of N, N- dimethylformamide. After an
20 hour the solvents were removed on the rotary evaporator. The 4-bromo crotonyl
chloride was taken up in 25 ml of tetrahydrofuran, and 3.39 grams of 6-Amino-4-(3-
bromo-phenylamino)-quinoline-3-carbonitrile in 25 ml of tetrahydrofuran was added
25 10 dropwise. This was followed by the dropwise addition of 1.92 ml (0.011 moles) of
diisopropylethylamine. After the addition of 25 ml of water and 50 ml of ethyl
acetate, the layers were separated. The organic layer was dried over anhydrous
30 15 sodium sulfate, and taken to a solid *in vacuo*. This solid was digested for an hour
with refluxing ethyl acetate then filtered from the ethyl acetate while still hot. Thus
was obtained 3.31 grams (68%) of 4-bromo-but-2-enoic acid [4-(3-bromo-
phenylamino)-3-cyano-quinolin-6-yl]-amide.

35 20 Example 16

2-Cyano-3-(2-methyl-4-nitrophenyl)acrylic Acid Ethyl Ester

40 40 A mixture of 2-methyl-4-nitroaniline (38.0 g, 250 mmol), ethyl (ethoxymethylene)-
cyanoacetate (50.8 g, 300 mmol), and 200 ml of toluene was refluxed for 24 h,
cooled, diluted with 1:1 ether-hexane, and filtered. The resulting white solid was
25 25 washed with hexane-ether and dried to give 63.9 g, mp 180-210°C.

45 45 Example 17

1,4-Dihydroquinoline-8-methyl-6-nitro-3-carbonitrile

50 50 A stirred mixture of 64 g (230 mmol) of 2-cyano-3-(2-methyl-4-nitrophenyl)acrylic
acid ethyl ester and 1.5 L of Dowtherm A was heated at 260°C for 12 h, cooled,

10 diluted with hexane, and filtered. The grey solid thus obtained was washed with hexane and dried to give 51.5 g, mp 295-305°C.

Example 18

15 4-Chloro-8-methyl-6-nitro-quinoline-3-carbonitrile

20 A stirred mixture of 1,4-dihydroquinoline-8-methyl-6-nitro-3-carbonitrile (47 g, 200 mmol) and 200 ml of phosphorous oxychloride was refluxed for 4 h. The phosphorous oxychloride was removed in vacuo, and the residue was stirred with methylene chloride at 0°C and treated with a slurry of ice and sodium carbonate. The 10 organic layer was separated and washed with water. The solution was dried and concentrated to a volume of 700 ml. The product was precipitated by the addition of hexane and cooling to 0°C. The white solid was filtered off and dried to give 41.6 g, 25 mp 210-212°C.

Example 19

30 4-[*(3-Bromophenyl)*amino]-8-methyl-6-nitro-quinoline-3-carbonitrile

35 A stirred mixture of 4-chloro-8-methyl-6-nitro-quinoline-3-carbonitrile (14.8 g, 60 mmol), 3-bromoaniline (12.4 g, 72 mmol), pyridine hydrochloride (6.93 g, 60 mmol), and 180 ml of ethoxyethanol was refluxed for 1.5 h, cooled, poured into a stirred mixture of water and an amount of sodium carbonate to give a pH of 8-9. The 20 resulting yellow solid was filtered, washed with water, dried, digested in boiling ether, filtered, and dried to give 22.6 g, mp 263-267°C.

Example 20

40 4-[*(3-Bromophenyl)*-N-acetylaminol]-8-methyl-6-nitro-quinoline-3-carbonitrile

45 A stirred mixture of 4-[*(3-bromophenyl)*amino]-8-methyl-6-nitro-quinoline-3-carbonitrile (15.3 g, 40 mmol), 0.37 g (3 mmol) of dimethylaminopyridine, 40 ml of acetic anhydride, and 80 ml of pyridine was refluxed for 3 h and concentrated at 50°C under vacuum. The residue was stirred with methylene chloride and 0.1 N HCl. After filtration through Celite, the organic layer was washed with water, dried and 50 concentrated. The residue was subjected to chromatography on silica gel with 1%

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10 acetic acid in methylene chloride to give 11.2 g of an amber glass, NMR (CDCl₃) δ 2.29 (N-acetyl group).

15 **Example 21**

- 5 8-Bromomethyl-4-[(3-bromophenyl)-N-acetylamino]-6-nitro-quinoline-3-carbonitrile
A stirred mixture of 4-[(3-bromophenyl)-N-acetylamino]-8-methyl-6-nitro-
quinoline-3-carbonitrile (10.6 g, 25 mmol), N-bromosuccinimide (6.68 g, 37.5
mmol), 0.30 g of dibenzoyl peroxide, and 200 ml of carbon tetrachloride was refluxed
for 2h, treated with an additional 0.30 g of dibenzoyl peroxide, and refluxed an
10 additional 2.5 h, cooled, diluted with methylene chloride, and stirred with aqueous
sodium bisulfite. The organic layer was separated and washed successively with
water, sodium bicarbonate solution, and water. The solution was dried and
25 evaporated to give 15 g of a white foam, NMR (CDCl₃) δ 5.19 (dd, CH₂Br).

15 **Example 22**

- 30 4-[(3-Bromophenyl)aminol]-8-dimethylaminomethyl-6-nitro-quinoline-3-carbonitrile
To a stirred solution of dimethylamine in THF (2.0 M; 115 ml; 230 mmol) at 0°C
was added a solution of 8-bromomethyl-4-[(3-bromophenyl)-N-acetylamino]-6-nitro-
quinoline-3-carbonitrile (11.6 g, 23 mmol) in 115 ml of THF during 15 m. After
35 warming to 25°C the mixture was stirred for 2h. The THF was evaporated off, and
20 the residue was refluxed in 230ml of methanol with 12.7 g (92 mmol) of potassium
carbonate for 1 h. The mixture was cooled, saturated with CO₂, and concentrated.
The residue was partitioned with methylene chloride and water. The organic layer
40 was washed with water, dried, and concentrated. The residue was subjected to
25 chromatography on silica gel with methylene chloride-ethyl acetate-methanol-
triethylamine to give 6.0 g yellow solid, mp 223-226°C.

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Example 23**6-Amino-4-[¹(3-bromophenyl)amino]-8-dimethylaminomethyl-quinoline-3-carbonitrile**

A stirred mixture of 4-[¹(3-bromophenyl)amino]-8-dimethylaminomethyl-6-nitro-5 quinoline-3-carbonitrile (5.98 g, 14.1 mmol), iron powder (2.76 g, 49 mg-atoms), acetic acid (5.67 ml, 99 mmol), and 70 ml of methanol was refluxed for 2 h and then evaporated to remove methanol. The residue was stirred with water for 10 m, and the orange solid was filtered off and washed with 2% acetic acid. The total filtrate was basified to pH 10 with 5 N sodium hydroxide. The resulting precipitate was extracted with methylene chloride. The extract was washed with water, dried, and concentrated. The residue was subjected to chromatography on silica gel with ethyl acetate-methanol-triethylamine to give 3.34 g of amber solid; mass spectrum (electrospray, m/e) M+H 396.2, 398.1.

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Example 24**6-Amino-4-[¹(3-iodophenyl)amino]-quinoline-3-carbonitrile**

A mixture of 6.70g (16.1 mmol) 4-[¹(3-iodophenyl)amino]-6-nitro-quinoline-3-carbonitrile, 300 ml ethanol, and 18.2 g (80.5 mmol) SnCl₂ dihydrate was heated to reflux under N₂. Removed heat at 2 hours, added ice water. Added sodium bicarbonate until pH was basic, forming a thick yellow mixture. Stirred for 2 1/2 hours. Extracted with chloroform, stirred organic portion with Darco and filtered through magnesium sulfate. Stripped solvent and dried in vacuo, giving 3.48g of yellow-brown solid: mass spectrum (electrospray m/e): M+H = 387.0.

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Example 25**4-[¹(3-Iodophenyl)amino]-6-nitro-quinoline-3-carbonitrile**

A mixture of 3.10 ml (25.7 mmol) 3-iodoaniline, 200 ml ethanol, and 5.00 g (21.4 mmol) 4-chloro-6-nitro-quinoline-3-carbonitrile was heated to reflux under N₂ for 3 1/2 hours. Cooled and made basic with a saturated sodium bicarbonate. Stripped solvents and azeotroped with ethanol. Slurried residue with hexane and collected. Air dried, washed solids with water, and dried in vacuo. Dissolved solids in 400 ml

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10 ethyl acetate, stirred with Darco, filtered and removed solvent. Dried solids in vacuo to give 7.38 g of yellow solid: mass spectrum (electrospray m/e): M+H = 417.0.

Example 26

- 15 **6-Amino-4-[(3-methylphenyl)aminol-quinoline-3-carbonitrile**
Added 253 mg 10% palladium on carbon to a round bottom flask under N₂ and covered catalyst with 140 ml ethanol. To this added 2.49 g (8.18 mmol) 6-nitro-4-[(3-methylphenyl)amino]-quinoline-3-carbonitrile and 640 µl (20.4 mmol) anhydrous hydrazine. The mixture was heated to reflux for 2 hours 15 minutes and filtered hot
20 through ccelite. Stripped solvent and dried in vacuo, giving 2.455 g of yellow solid: mass spectrum (electrospray m/e): M+H = 275.2.

Example 27

- 30 **6-Nitro-4-[(3-methylphenyl)aminol-quinoline-3-carbonitrile**
15 A mixture of 5.00 g (21.5 mmol) 4-chloro-6-nitro-quinoline-3-carbonitrile, 200 ml ethanol, and 2.75 ml (25.7 mmol) 3-toluidine was heated to reflux for 4 ½ hours. Cooled and added a saturated sodium bicarbonate until pH was basic. Stripped solvents and azeotroped with ethanol. Slurried with hexane, collected, and air dried. Washed with water and dried in vacuo. Boiled in ethyl acetate, stirred with Darco
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20 and filtered. Stripped solvent and dried in vacuo to give 4.82 g of yellow-orange solid: mass spectrum (electrospray m/e): M+H = 305.2.

Example 28

- 45 **6-Amino-4-[(3-chlorophenyl)aminol-quinoline-3-carbonitrile**
25 A mixture of 6.30 g (19.4 mmol) 4-[(3-chlorophenyl)amino]-6-nitro-quinoline-3-carbonitrile, 300 ml ethanol, and 21.9 g (97 mmol) SnCl₂ dihydrate were heated to reflux under N₂. Removed heat at 2 ½ hours, added ice water and made basic with sodium bicarbonate. Stirred for 2 hours and extracted with chloroform. Dried organic layer with sodium sulfate, filtered, stripped solvent and dried residue in
50
30 vacuo, giving 5.74 g of yellow-brown solid: mass spectrum (electrospray m/e): M+H = 295.1, 297.1.

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Example 29

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4-[3-Chlorophenyl]amino]-6-nitro-quinoline-3-carbonitrile

15

A mixture of 10.0 g (42.9 mmol) 4-chloro-6-nitro-quinoline-3-carbonitrile, 260 ml ethanol, and 5.40 ml 3-chloroaniline was heated to reflux under N₂. Removed heat at

20

5 hours, cooled to 25°C and added saturated sodium bicarbonate until the pH was basic. Stripped solvents and azeotroped with ethanol. Slurried residue with hexane, collected solid, and air dried. Washed solids with water and dried in vacuo. Dissolved in boiling ethyl acetate, stirred with Darco, and filtered. Stripped solvent and dried residue in vacuo, giving 6.5g of yellow solid: mass spectrum (electrospray m/e): M+H = 325.0, 327.0.

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Example 306-Amino-4-[3-methoxyphenyl]amino]-quinoline-3-carbonitrile

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325 mg of 10% palladium on carbon was added to a round bottom flask under N₂, and covered with 165 ml ethanol. Added 3.29 g (10.3 mmol) 4-[3-methoxyphenyl]-amino]-6-nitro-quinoline-3-carbonitrile and 800μl anhydrous hydrazine and heated mixture to reflux. At 1 ½ hours, filtered hot through celite, stripped solvent and dried in vacuo, giving 2.876 g of yellow solid: mass spectrum (electrospray m/e): M+H = 291.2.

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20

Example 314-[3-methoxyphenyl]amino]-6-nitro-quinoline-3-carbonitrile

40

A mixture of 5.00 g (21.5 mmol) 4-chloro-6-nitro-quinoline-3-carbonitrile, 200 ml ethanol, and 3.0 ml (26.0 mmol) m-anisidine was heated to reflux under N₂.

45

25 Removed heat at 4 ½ hours and made basic with saturated sodium bicarbonate. Stripped solvents and azeotroped with ethanol. Slurried with hexane and collected crystals. Washed with water, dried in vacuo. Dissolved 5.94 g of crude product in 320 ml boiling ethyl acetate, stirred with Darco, filtered, stripped solvent, and dried in vacuo, giving about 5 g of yellow-orange solid: mass spectrum (electrospray m/e):

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30 M+H = 291.1.

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Example 32

- 10 6-Amino-4-[(3-chloro-4-fluorophenyl)amino]-quinoline-3-carbonitrile
A mixture of 5.360 g (15.6 mmol) 4-[(3-chloro-4-fluorophenyl)amino]-6-nitro-
15 quinoline-3-carbonitrile, 250 ml ethanol, and 17.67 g (78.2 mmol) SnCl₂ dihydrate
5 was heated to reflux under N₂. Removed heat at 1 ½ hours and added ice water.
Made basic with sodium bicarbonate. Stirred for 2 hours extracted with chloroform.
20 Added brine to the separatory funnel to help separate layers. Stirred organic layer
with Darco and dried with sodium sulfate. Filtered, stripped solvent and dried in
vacuo, giving 4.460 g of yellow-brown solid: mass spectrum (electrospray m/e):
25 10 M+H = 312.9, 315.0.

Example 33

- 25 4-[(3-chloro-4-fluorophenyl)amino]-6-nitro-quinoline-3-carbonitrile
A mixture of 5.00 g (21.5 mmol) 4-chloro-6-nitro-quinoline-3-carbonitrile, 200 ml
15 ethanol, and 3.75 g (25.8 mmol) 3-chloro-4-fluoroaniline was heated to reflux under
30 N₂. Removed heat at 3 ½ hours and added a solution of saturated sodium bicarbonate
until mixture was basic. Stripped solvents and azeotroped with ethanol. Slurried
residue with hexane, collected solids, washed with water and dried in vacuo.
35 Dissolved solids in 250 ml boiling ethyl acetate, stirred with Darco, and filtered.
20 Stripped solvent and dried in vacuo, giving 6.036 g of yellow solid: mass spectrum
(electrospray m/e): M+H = 343.1, 345.1.

Example 34

- 40 6-Amino-4-[(4-bromophenyl)aminol]-quinoline-3-carbonitrile
25 A mixture of 3.10 g (8.40 mmol) 4- [(4-bromophenyl)amino]-6-nitro-quinoline-3-
carbonitrile, 155 ml ethanol, and 9.47 g (42.0 mmol) SnCl₂ dihydrate was heated to
45 reflux under N₂. After 4 hours, removed heat and added ice water. Made basic with
sodium bicarbonate and stirred for 2 hours. With mixture still basic, extracted with
chloroform, stirred organic layer with Darco and dried with sodium sulfate. Filtered,
50 stripped solvent and dried in vacuo, giving 2.265 g of brown-yellow solid: mass
spectrum (electrospray m/e): M+H = 339.0, 341.0.

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Example 35

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4-[*(4-Bromophenyl)amino*]-6-nitro-quinoline-3-carbonitrile

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A mixture of 5.00 g (21.5 mmol) 4-chloro-6-nitro-quinoline-3-carbonitrile, 200 ml ethanol, and 4.42 g (25.8 mmol) p-bromoaniline was heated to reflux under N₂ for 3 hours. Removed heat and added saturated sodium bicarbonate until basic. Stripped solvents and azeotroped with ethanol. Slurried residue with hexane, collected solids, and air dried. Washed with water and dried in vacuo. Boiled in 1.4 liters ethyl acetate, and without completely dissolving all solids, stirred with Darco, and filtered. Stripped solvent and dried in vacuo, giving 3.524 g of yellow solid: mass spectrum (electrospray m/e): M+H = 369, 370.9.

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Example 366-Amino-4-[*(3,4-difluorophenyl)amino*]-quinoline-3-carbonitrile

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A mixture of 4.53 g (13.9 mmol) 4-[*(3,4-difluorophenyl)amino*]-6-nitro-quinoline-3-carbonitrile, 200 ml ethanol and 15.72 g (69.4 mmol) SnCl₃ dihydrate was heated to reflux under N₂. Removed heat at 1 1/2 hours, added ice water and made basic with sodium bicarbonate. Stirred for 2 hours and extracted with chloroform. Stirred organic layer with Darco, dried with sodium sulfate and filtered. Stripped solvent and dried in vacuo, giving 3.660 g of yellow-green solid: mass spectrum (electrospray m/c): M+H = 297.1.

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Example 374-[*(3,4-Difluorophenyl)amino*]-6-nitro-quinoline-3-carbonitrile

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A mixture of 5.00 g (21.5 mmol) 4-chloro-6-nitro-quinoline-3-carbonitrile, 250 ml ethanol and 2.55 ml (25.8 mmol) 3,4-difluoroaniline was heated to reflux under N₂. Removed heat at 3 1/2 hours and made basic with saturated sodium bicarbonate. Stripped solvents and azeotroped with ethanol. Slurried residue with hexane, collected solids and air dried. Washed with water and dried in vacuo. Dissolved in ethyl acetate, stirred with Darco, filtered, stripped solvent and dried in vacuo, giving 5.02 g of yellow solid: mass spectrum (electrospray m/e): M+H = 327.1.

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Example 38**6-Amino-4-[(3-chloro-4-thiophenoxyphenyl)amino]-quinoline-3-carbonitrile**

A mixture of 6.753 g (15.6 mmol) 4-[(3-chloro-4-thiophenoxyphenyl)amino]-6-nitro-quinoline-3-carbonitrile, 250 ml ethanol, and 17.66 g (78.0 mmol) SnCl_2 dihydrate was heated to reflux under N_2 . Removed heat at 2 hours, added large volume of ice water, and made basic with sodium bicarbonate. Stirred for 2 hours and with mixture still basic, extracted with chloroform. Stirred organic layer with Darco, dried with sodium sulfate, filtered, stripped solvent and dried in vacuo, giving 5.996 g of yellow-brown solid: mass spectrum (electrospray m/e): $M+H = 403.1, 405.1$.

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Example 39**4-[(3-Chloro-4-thiophenoxyphenyl)aminol-6-nitro-quinoline-3-carbonitrile**

A mixture of 5.00 g (21.5 mmol) 4-chloro-6-nitro-quinoline-3-carbonitrile, 250 ml ethanol, and 6.07 g (25.6 mmol) 3-chloro-4-thiophenoxyaniline was heated to reflux under N_2 . Removed heat at about 8 hours, made basic with saturated sodium bicarbonate, stripped solvents and azeotroped with ethanol. Slurried residue with hexane and collected solids. Washed with water and dried in vacuo. Dissolved nearly completely in 400 ml ethyl acetate, stirred with Darco and filtered. Stripped solvent and boiled in hexane to remove last of the excess aniline. Dried in vacuo, giving 6.90 g of red solid: mass spectrum (electrospray m/e): $M+H = 433.1, 435.1$.

Example 40**6-Amino-4-[(3-cyanophenyl)aminol-quinoline-3-carbonitrile**

Added 100 mg of 10% palladium on carbon to a round bottom flask under N_2 and covered with 50 ml ethanol. Added 1.00g (3.17 mmol) 4-[(3-cyanophenyl)amino]-6-nitro-quinoline-3-carbonitrile and 250 μl (7.39 mmol) anhydrous hydrazine and heated to reflux. Removed heat at 2 hours and filtered hot through celite. Stripped solvent and dried in vacuo, giving 887 mg of yellow solid: mass spectrum (electrospray m/e): $M+H = 286.2$.

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Example 41

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4-[(3-Cyanophenyl)amino]-6-nitro-quinoline-3-carbonitrile

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A mixture of 5.00 g (21.5 mmol) 4-chloro-6-nitro-quinoline-3-carbonitrile, 200 ml ethanol, and 3.04 g (25.8 mmol) 3-aminobenzonitrile was heated to reflux. Removed
5 heat at 3 ½ hours and made basic with saturated sodium bicarbonate. Stripped solvents and air dried. Slurried residue with hexane and collected solids. Washed with water and dried in vacuo. Boiled in large volume ethyl acetate, collected solids and dried in vacuo, giving 5.15 g of yellow-brown solid: mass spectrum (electrospray m/e): 316.0.

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Example 42

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6-Amino-4-[(3-ethynylphenyl)amino]-quinoline-3-carbonitrile

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A mixture of 2.00g (6.36 mmol) 4-[(3-ethynylphenyl)amino]-6-nitro-quinoline-3-carbonitrile, 100 ml ethanol, and 7.19 g (31.8 mmol) SnCl₂ dihydrate was heated to reflux under N₂. Removed heat at 3 ½ hours and added ice water. Made basic with sodium bicarbonate and stirred for 2 hours. Extracted with chloroform, stirred organic layer with Darco, dried with sodium sulfate, filtered, stripped solvent, and dried in vacuo, giving 1.737 g of yellow-brown solid: mass spectrum (electrospray m/e): M+H = 285.2.

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Example 43

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4-[(3-Ethynylphenyl)amino]-6-nitro-quinoline-3-carbonitrile

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A mixture of 5.00 g (21.5 mmol) 4-chloro-6-nitro-quinoline-3-carbonitrile, 200 ml ethanol, and 3.82 g (32.6 mmol) 3-ethynylaniline was heated to reflux under N₂.
25 Removed heat at 3 ½ hours and added a solution of saturated sodium bicarbonate until basic. Stripped solvents and azeotroped with ethanol. Slurried residue with hexane and collected solids. Washed with water and dried in vacuo. Dissolved in ethyl acetate, stirred with Darco, filtered, stripped solvent and dried in vacuo, giving 4.544 g of yellow solid: mass spectrum (electrospray m/e): M+H = 315.1.

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Example 44**4-[3-Bromo-4-fluorophenyl]aminol-6-nitro-quinoline-3-carbonitrile**

A mixture of 3.8g (16.33mmol) of 4-chloro-6-nitro-quinoline-3-carbonitrile and 3.7g (20mmol) of 3-bromo-4-fluoroaniline in 200mL of ethanol was refluxed for 3hr.

5 After the solvent was removed, the residue was dissolved in ethyl acetate and washed with sodium bicarbonate. The product was collected as a pale yellow solid, 6.5g (71%); ESMS m/z 387.3, 389.2, mp 269-270°C (dec).

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Example 45**6-amino-4-[3-Bromo-4-fluorophenyl]aminol- quinoline -3-carbonitrile**

A mixture of 8g (20.67mmol) of 4-[(3-chloro-4-fluorophenyl)amino]-6-nitro-

25 quinoline-3-carbonitrile, 4g (72.35mmol) of iron dust and 8.9g (165.36mmol) of ammonium chloride in 240mL of methanol and water (2:1 ratio) was refluxed for 4hr.

The mixture was filtered hot and washed with methanol and water. The product 15 precipitated from the filtrate upon cooling. The solid was collected and dried in 30 vacuo to give 5.8g (79%) yellowish brown solid; ESMS m/z 356.8, 358.8, mp 210-212°C.

Example 46**4-(3-Chloro-4-fluoro-phenylamino)-7-methoxy-6-nitro-quinoline-3-carbonitrile**

35 20 A mixture of 4.4 g (16.7 mmol) of 4-chloro-7-methoxy -6-nitro-quinoline-3-carbonitrile and 2.67 g (18.3 mmol) of 3-chloro-4-fluoro aniline in 110 ml of methoxyethanol was refluxed under nitrogen for 4 hours. The reaction mixture was

40 diluted with ethyl acetate and wash with sodium bicarbonate solution and sodium chloride solution. The organic layer was dried over sodium sulfate and then the

25 solvent was removed under vacuum. The residue was chromatographed on silica gel eluting with mixture of ethyl acetate and methanol to give 3 g yellow solid: mass spectrum (electrospray, m/e): 372.9.

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Example 47

6-Amino-4-(3-chloro-4-fluoro-phenylamino)-7-methoxy-quinoline-3-carbonitrile

A mixture of 4.88 g (13 mmol) of 4-[(3-chloro-4-fluorophenyl)amino]-7-methoxy-6-nitro-quinoline-3-carbonitrile, 5.2 g (97.5 mmol) of ammonium chloride, and 3.3 g (58.5 mmol) iron was stirred at reflux in 60 ml of water and 60 ml of methanol for 4.5 hours. The mixture was diluted with 500 ml of hot ethyl acetate and the hot mixture was filtered. The filtration was washed with saturated sodium chloride solution and then the organic layer was dried over sodium sulfate. The solvent was removed and the residue was chromatographed on silica gel eluting with mixture of ethyl acetate and methanol to give 3.38 g of yellow solid: mass spectrum (electrospray, m/e): M+H 343.4.

Example 48

4-(3-Bromo-4-fluoro-phenylamino)-7-methoxy-6-nitro-quinoline-3-carbonitrile

A mixture of 3.52 g (9.7 mmol) of 4-chloro-7-methoxy-6-nitro-quinoline-3-carbonitrile and 2.0 g (10.7 mmol) of 3-bromo-4-fluoro aniline in 150 ml of methoxyethanol was refluxed under nitrogen for 5.5 hours. The reaction mixture was diluted with ethyl acetate and wash with sodium bicarbonate solution and sodium chloride solution. The organic layer was dried with sodium sulfate and then solvent was removed under vacuum. The residue was chromatographed on silica gel eluting with mixture of ethyl acetate and hexane to give the title compound.

Example 49

6-Amino-4-(3-bromo-4-fluoro-phenylamino)-7-methoxy-quinoline-3-carbonitrile

A mixture of 2.9 g (6.95 mmol) of 4-[(3-bromo-4-fluorophenyl)amino]-7-methoxy-6-nitro-quinoline-3-carbonitrile, 6.5 g (121.6 mmol) of ammonium chloride and 4.05 g (73 mmol) of iron in 50 ml of water and 50 ml of methanol for 6 hours. The mixture was diluted with hot ethyl acetate and the hot mixture was filtered. The filtration was washed with saturated sodium chloride solution then the organic layer was dried over sodium sulfate. The solvent was removed and the residue was chromatographed on

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silica gel eluting with mixture of ethyl acetate and methanol to give 2.11 g of light yellow solid: mass spectrum (electrospray, m/c): M+H 386.7 and 388.8.

10 Example 50

15 7-Ethoxy-4-hydroxy-quinoline-3-carbonitrile

A mixture of 10 g (73 mmol) of 3-ethoxy aniline and 12.3 g (73 mmol) of ethyl (ethoxymethylene) cyanoacetate was heated in 90 ml of Dowther at 140°C for 7 hours. To this mixture was added 250 ml of Dowther. The solution was stirred and refluxed under nitrogen for 12 hours with periodically distilling out the eliminated ethanol. The mixture was cooled to room temperature and the solid was collected and washed with hexane. The crude solid was treated with boiling ethanol and then filtered to give 9.86 g of brown solid: mass spectrum (electrospray, m/c): M+H 214.7.

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10 was removed giving 2.1 g of beige solid: mass spectrum (electrospray, m/e) M+H
277.7.

Example 53

15 **4-(3-Bromo-phenylamino)-7-ethoxy-6-nitro-quinoline-3-carbonitrile**
A mixture of 2.1 g (7.6 mmol) of 4-chloro-7-ethoxy-6-nitro-quinoline-3-carbonitrile
and 0.91 ml (8.3 mmol) of 3-bromo aniline in 100 ml ethanol was refluxed under
nitrogen for 4.5 hours. The reaction mixture was poured into diluted sodium
bicarbonate solution. Ethanol was removed under vacuum. The mixture was diluted
20 with ethyl acetate and the organic layer was separated and dried over sodium sulfate.
The solution was concentrated and solid was collected and then washed with hexane.
Upon drying, 2.6 g of yellow solid obtained: mass spectrum (electrospray, m/e) M+H
25 412.8 and 414.9.

15 **Example 54**

30 **6-Amino-4-(3-bromo-phenylamino)-7-ethoxy-quinoline-3-carbonitrile**
A mixture of 2.5 g (6 mmol) of 4-[(3-bromophenyl)amino]-7-ethoxy-6-nitro-
quinoline-3-carbonitrile, 2.4 g (45 mmol) of ammonium chloride, and 1.5 g (27
mmol) iron was stirred at reflux in 40 ml of water and 40 ml of methanol for 4 hours.
35 20 The mixture was diluted with 500 ml of hot ethyl acetate and the hot mixture was
filtered. The filtration was washed with saturated sodium chloride solution and then
the organic layer was dried over sodium sulfate. The solution was concentrated and
40 1.5 of beige solid was collected: mass spectrum (electrospray, m/e): M+H 382.8 and
384.8.

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Example 55

45 **8-Methoxy-4-hydroxy-6-nitro-quinoline-3-carbonitrile**
A mixture of 12.6 g (75 mmol) of 2-methoxy-4-nitro aniline and 12.7 g (75 mmol)
of ethyl (ethoxymethylene) cyanoacetate was heated in 100 ml of Dowther at 120°C
50 30 for overnight and 180°C for 20 hours. To this mixture was added 300 ml of Dowther.
The solution was stirred and refluxed under nitrogen for 12 hours with periodically

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distilling out the eliminated ethanol. The mixture was cooled to room temperature and the solid was collected and washed with hexane. The crude solid was treated with boiling ethanol and then filtered to give 12 g of brown solid: mass spectrum (electrospray, m/e): M+H 245.8.

Example 56

4-Chloro-8-methoxy-6-nitro-quinoline-3-carbonitrile

A mixture of 4 g (16 mmol) of 8-Methoxy-4-hydroxy-6-nitro-quinoline-3-carbonitrile, 6.66 g (32 mmol) of phosphorous pentachloride, and 15 ml of

10 phosphorous oxychloride was refluxed for 2.5 hours. The mixture was diluted with hexane and the solid was collected. The solid was dissolved in 500 ml of ethyl acetate and washed with cold diluted sodium hydroxide solution. The solution was dried over magnesium sulfate and filtered through a pad of silica gel. The solvent was removed giving 2.05 g of tan solid: mass spectrum (electrospray, m/e) M+H

15 263.7.

Example 57

6-nitro-4-(3-bromo-phenylamino)-8-methoxy-quinoline-3-carbonitrile

A mixture of 1.9 g (7.6 mmol) of 4-chloro-8-methoxy-6-nitro-quinoline-3-

35 carbonitrile and 0.86 ml (8.3 mmol) of 3-bromo aniline in 95 ml ethanol was refluxed under nitrogen for 5 hours. The reaction mixture was poured into diluted sodium bicarbonate solution. Ethanol was removed under vacuum. The mixture was diluted with ethyl acetate and the organic layer was separated and dried over sodium chloride. The solution was concentrated and solid was collected and then washed
20 with hexane. Upon drying, 2.3 g of yellow solid obtained: mass spectrum (electrospray, m/e) M+H 398.8 and 400.8.

Example 58

6-Amino-4-(3-bromo-phenylamino)-8-methoxy-quinoline-3-carbonitrile

30 A mixture of 2.15 g (5 mmol) of 4-[(3-bromophenyl)amino]-8 -methoxy-6-nitro-quinoline-3-carbonitrile, 1.95 g (37.5 mmol) of ammonium chloride, and 1.26 g (22.5

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mmol) iron was stirred at reflux in 40 ml of water and 40 ml of methanol for 3 hours.

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The mixture was diluted with 500 ml of hot ethyl acetate and the hot mixture was filtered. The filtration was washed with saturated sodium chloride solution and then the organic layer was dried over sodium sulfate. The solution was concentrated and

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5 0.43 of dark yellow solid was collected: mass spectrum (electrospray, m/e): M+H 368.9 and 370.9.

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Example 594-Chloro-but-2-yanoic acid

10 Propargyl chloride (2 mL, 26.84mmol) was dissolved in 40 mL of tetrahydrofuran under nitrogen and cooled to -78°C. After addition of n-butyllithium (5.4 mL, 13.42mmol, 2.5 M in n-hexane) and stirred for 15 min, a stream of dry carbon dioxide was passed through it at -78°C for two hours. The reaction solution was filtered and neutralized with 3.5 mL of 10% sulfuric acid. After evaporation of the 15 solution, the residue was extracted with ether. The ether solution was washed with saturated brine solution, and dried over sodium sulfate. After evaporation of the dry 30 ether solution, 0.957g (60%) of an oil product was obtained: ESMS m/z 116.6 (M-H⁺).

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Example 604-Dimethylamino -but-2-yanoic acid

n-Butyl lithium in hexane (96mL, 2.5 M in n-hexane) was slowly added to 1-dimethylamino-2-propyne (20g, 240mmol) in 100 mL of tetrahydrofuran under 40 nitrogen. The mixture was stirred for 1 h at -78°C, then dry carbon dioxide was pass 25 through overnight. The resulting solution was poured into water and washed with ethyl acetate. The aqueous layer was evaporated under reduced pressure to give the 45 crude acid. The dry acid was dissolved in methanol, and the insoluble salt was removed via filtration. The filtrate was collected and dried in vacuo to give 15.6g of 4-dimethylamino -but-2-yanoic acid: mass spectrum (m/e):M-H 126.

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Example 61

Bis-(2-methoxy-ethyl)-prop-2-ynyl-amine

Propargyl bromide (17.8g, 150mmol) was added dropwise to a mixture of bis(2-methoxy-ethyl)amine (20g, 150mmol) and cesium carbonate (49g, 150mmol) in 350mL of acetone. The mixture was stirred overnight under nitrogen at room temperature. The inorganic salts were then filtered off, and the solvent was removed. The residue was dissolved in saturated sodium bicarbonate solution and extracted with ethyl acetate. The organic extracts were then evaporated to give 20g of bis-(2-methoxy-ethyl)-prop-2-ynyl-amine: mass spectrum (m/e): M+H 172.

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Example 62

4-[Bis-(2-methoxy-ethyl)-amino]-but-2-yneic acid

n-Butyl lithium in hexane (42mL, 2.5M in n-hexane) was slowly added to bis-(2-methoxy-ethyl)-prop-2-ynyl-amine (18g, 105mmol) in 80mL of tetrahydrofuran under nitrogen. The mixture was stirred for 1 h at -78°C, then dry carbon dioxide was passed through overnight. The resulting solution was poured into water and washed with ethyl acetate. The aqueous layer was evaporated under reduced pressure to give the crude acid. The dry acid was dissolved in methanol, and the insoluble salt was removed via filtration. The filtrate was collected and dried in vacuo to give 18g of 4-[bis-(2-methoxy-ethyl)-amino]-but-2-yneic acid: mass spectrum (m/e):M-H 214.

Example 63

1-Methyl-4-prop-2-ynyl-piperazine

Propargyl bromide (23.8g, 200mmol) was added dropwise to a mixture of 1-methyl-piperazine (20g, 200mmol) and cesium carbonate (65g, 200mmol) in 350mL of acetone. The mixture was stirred overnight under nitrogen at room temperature. The inorganic salts were then filtered off, and the solvent was removed. The residue was dissolved in saturated sodium bicarbonate solution and extracted with ethyl acetate. The organic extracts were then evaporated to give 7.5g of 1-methyl-4-prop-2-ynyl-piperazine: mass spectrum (m/e): M+H 139.

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Example 64

10 4-(4-Methyl-piperazin-1-yl)-but-2-ynoic acid

n-Butyl lithium in hexane (17.2mL, 2.5M in n-hexane) was slowly added to
1-methyl-4-prop-2-ynyl-piperazine (6.0g, 43.5mmol) in 40mL of tetrahydrofuran
15 under nitrogen. The mixture was stirred for 1 hr at -78°C, then dry carbon dioxide
was passed through overnight. The resulting solution was poured into water and
washed with ethyl acetate. The aqueous layer was evaporated under reduced pressure
20 to give the crude acid. The dry acid was dissolved in methanol, and the insoluble salt
was removed via filtration. The filtrate was collected and dried in vacuo to give 7g of
10 4-(4-methyl-piperazin-1-yl)-but-2-ynoic acid: mass spectrum (m/e):M-H 181.

Example 65

25 (2-Methoxy-ethyl)-methyl-prop-2-ynyl-amine

Propargyl bromide (26.8g, 225mmol) was added dropwise to a mixture of N-
15 (2-methoxyethyl)methyl amine (20g, 225mmol) and cesium carbonate (73g,
30 225mmol) in 350mL of acetone. The mixture was stirred overnight under nitrogen at
room temperature. The inorganic salts were then filtered off, and the solvent was
removed. The residue was dissolved in saturated sodium bicarbonate solution and
35 extracted with ethyl acetate. The organic extracts were then evaporated to give 14g of
20 (2-methoxy-ethyl)-methyl-prop-2-ynyl-amine: mass spectrum (m/e): M+H 127.

Example 66

40 4-[(2-Methoxy-ethyl)-methyl-amino]-but-2-ynoic acid

n-Butyl lithium in hexane (37.8mL, 2.5 M in n-hexane) was slowly added to
25 (2-methoxy-ethyl)-methyl-prop-2-ynyl-amine (12.0g, 94.5mmol) in 90mL of
45 tetrahydrofuran under nitrogen. The mixture was stirred for 1 hr at -78°C, then dry
carbon dioxide was passed through overnight. The resulting solution was poured into
water and washed with ethyl acetate. The aqueous layer was evaporated under
reduced pressure to give the crude acid. The dry acid was dissolved in methanol, and
50 the insoluble salt was removed via filtration. The filtrate was collected and dried in

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vacuo to give 15g of 4-[(2-methoxy-ethyl)-methyl-amino]-but-2-yonoic acid: mass spectrum (m/e): M-H 170.

10 Example 67

15 Allyl-methyl-prop-2-ynyl-amine

Propargyl bromide (33.4g, 281mmol) was added dropwise to a mixture of isopropyl-methyl- amine (20g, 281mmol) and cesium carbonate (90g, 281mmol) in 350mL of acetone. The mixture was stirred overnight under nitrogen at room temperature. The inorganic salts were then filtered off, and the solvent was removed.

20 10 The residue was dissolved in saturated sodium bicarbonate solution and extracted with ethyl acetate. The organic extracts were then evaporated to give 4.6g of allyl-methyl-prop-2-ynyl-amine: mass spectrum (m/c): M+H 110.

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Example 68

15 4-(Allyl-methyl-amino)-but-2-yonoic acid

n-Butyl lithium in hexane (16.4mL, 2.5M in n-hexane) was slowly added to allyl-methyl-prop-2-ynyl-amine (4.5g, 46mmol) in 50 mL of tetrahydrofuran under nitrogen. The mixture was stirred for 1 hr at -78°C, then dry carbon dioxide was passed through overnight. The resulting solution was poured into water and washed with ethyl acetate. The aqueous layer was evaporated under reduced pressure to give the crude acid. The dry acid was dissolved in methanol, and the insoluble salt was removed via filtration. The filtrate was collected and dried in vacuo to give 4.1g of 4-(allyl-methyl-amino)-but-2-yonoic acid: mass spectrum (m/e): M-H 152.

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25 Example 69

45 4-Methoxymethoxy-but-2-yonoic acid

To a suspension of 8.2 g of 60% sodium hydride in mineral oil in 271 mL of tetrahydrofuran at 0°C with stirring under nitrogen was added dropwise 10 g of propargyl alcohol over 15 min. The mixture was stirred an additional 30 min. To the 50 30 stirred mixture at 0°C was added 15.8 g of chloromethylmethyl ether. Stirring was continued at room temperature over night. The mixture was filtered and the solvent

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10 was removed from the filtrate. The residue was distilled (35-38°C, 4 mm) giving 8.5 g of a liquid. The distillate was dissolved in 200 mL of ether. The solution was stirred under nitrogen and cooled to -78°C as 34.1 mL of 2.5 molar n-butyl lithium in hexanes was added over 15 min. Stirring was continued for another 1.5 hr. Dry
15 5 carbon dioxide was allowed to pass over the surface of the stirring reaction mixture as it warmed from -78°C to room temperature. The mixture was stirred under a carbon dioxide atmosphere over night. The mixture was poured into a mixture of 14 mL of hydrochloric acid and 24 mL of water. The organic layer was separated and dried
20 over magnesium sulfate. The solvent was removed and the residue was maintained at 10 100°C at 4 mm for 1 hr giving 10.4 g 4-Methoxymethoxy-but-2-yneic acid.

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Example 70**4-Bromo crotonic acid**

After the method of Braun [Giza Braun, J. Am. Chem. Soc. 52, 3167 (1930)],
15 11.76 mL (17.9 grams 0.1 moles) of methyl 4-bromo crotonate in 32 mL of ethanol and 93 mL of water was cooled to -11 °C. The reaction was stirred vigorously, and
30 15.77 g (0.05 moles) of finely powdered barium hydroxide was added portionwise over a period of about an hour. Cooling and vigorous stirring were continued for about 16 hours. The reaction mixture was then extracted with 100 mL of ether. The
35 20 aqueous layer was treated with 2.67 mL (4.91 g; 0.05 moles) of concentrated sulfuric acid. The resulting mixture was extracted with 3-100 mL portions of ether. The combined ethereal extracts were washed with 50 mL of brine, then dried over sodium sulfate. The solution was taken to an oil *in vacuo*. This oil was taken up in about 400 mL of boiling heptane, leaving a gum. The heptane solution was separated and
40 25 boiled down to about 50mL. Cooling gave 3.46 g of product.

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Example 71**4-(2-Methoxy-ethoxy)-but-2-yneic acid**

To a suspension of 6.04 g (151 mmol) of 60% sodium hydride in 200 ml of
50 30 tetrahydrofuran at 0 °C was add 10 g (131.4 mmol) of 2-methoxyethanol dropwise over 15 min. After 1 hr, 19.54 g (131.4 mmol) of 80% propargyl bromide was added

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dropwise. After stirring 17 hr at room temperature, the mixture was filtered and the solvent was removed. The residue was distilled (48-51 °C, 4mm) to give 11.4 g of a colorless liquid. This was dissolved in 250 ml of ether and cooled to -78 °C with stirring under nitrogen. To this solution was added 39.95 ml (99.9 mmol) of 2.5M n-
5 butyl lithium solution in hexanes dropwise over 15 min. After 1.5 hr, dry carbon dioxide was bubbled in as the mixture slowly warmed to room temperature. The mixture was maintained in a carbon dioxide atmosphere overnight. To the mixture was added 100 ml of 3N hydrochloric acid and solid sodium chloride. The organic layer was separated and dried over magnesium sulfate. The solvent was removed and
10 the residue was maintained under vacuum giving 11.4 g of the title compound. : mass spectrum (electrospray, m/e, negative mode): M-H 156.8.

Example 72

4-(2-Methoxy-ethoxy)-but-2-yonoic acid [4-(3-bromo-phenylamino)-3- cyano-
quinolin-6-yl]-amide

To a solution of 0.56 g (3.54 mmol) of 4-(2-methoxy-ethoxy)-but-2-yonoic acid and 0.46 g (3.4 mmol) of isobutyl chloroformate in 12 ml of tetrahydrofuran was added at 0°C with stirring 0.36 g (3.54 mmol) of N-methylmorpholine. After 15 min, 1.0 g (2.95 mmol) of 6-amino-4-[(3-bromophenyl)amino]-quinoline-3-carbonitrile was
15 added. After stirring 3 hr at 0°C and 17 hr at room temperature, the mixture was poured into a saturated solution of sodium bicarbonate. The mixture was extracted with ethyl acetate and the organic layer was dried over magnesium sulfate. The solvent was removed and the residue was purified by chromatography on silica gel eluting with chloroform- ethyl acetate mixtures to give 0.53 g of 4-(2-Methoxy-
20 ethoxy)-but-2-yonoic acid [4-(3-bromo-phenylamino)-3- cyano-quinolin-6-yl]-amide
25 as a yellow powder: mass spectrum (electrospray, m/e,): M+H 480.9.

Example 73

4-(Methoxymethoxy)-but-2-yonoic acid

30 To a suspension of 8.2 g (205 mmol) of 60% sodium hydride in 271 ml of tetrahydrofuran was added dropwise at 0 °C with stirring 10.0 g (178.4 mmol) of

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propargyl alcohol . After 30 min, 15.8 g (196.2 mmol) of chloromethylmethyl ether was added. After stirring over the weekend at room temperature, the mixture was filtered and the solvent was remove. The residue was distilled (35-38 °C, 4mm) to give 8.54 g of a colorless liquid. This was dissolved in 200 ml of ether and cooled to -78 °C with stirring under nitrogen. To this solution was added 34.1 ml (85.3 mmol) of 2.5M n-butyl lithium solution in hexanes dropwise over 15 min. After 1.5 hr, dry carbon dioxide was bubbled in as the mixture slowly warmed to room temperature. The mixture was maintained in a carbon dioxide atmosphere overnight. To the mixture was added 14 ml of hydrochloric acid in 24 ml water. The organic layer was separated and dried over magnesium sulfate. The solvent was removed and the residue was maintained under vacuum giving 10.4 g of the title compound as a liquid.

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Example 744-Methoxymethoxy-but-2-yneic acid [4-(3-bromo-phenylamino)-3-cyano- quinolin-6-yl]-amide

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To a solution of 0.51 g (3.54 mmol) of 4-(methoxymethoxy)-but-2-yneic acid and 0.46 g (3.4 mmol) of isobutyl chloroformate in 12 ml of tetrahydrofuran was added at 0°C with stirring 0.36 g (3.54 mmol) of N-methylmorpholine. After 15 min, 1.0 g (2.95 mmol) of 6-amino-4-[(3-bromophenyl)amino]-quinoline-3-carbonitrile was added. After stirring 3 hr at room temperature, the mixture was poured into a saturated solution of sodium bicarbonate. The mixture was extracted with ethyl acetate and the organic layer was dries over magnesium sulfate. The solvent was remove and the residue was purified by chromatography on silica gel eluting with chloroform- ethyl acetate mixtures to give 0.66g of 4-methoxymethoxy-but-2-yneic acid [4-(3-bromo-phenylamino)-3-cyano- quinolin-6-yl]-amide as a yellow powder: ma of 6-amino-4-[(3-bromophenyl)amino]-quinoline-3-carbonitrile :mass spectrum (electrospray, m/e): M+H 465.1, 467.0.

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Example 75

N-[4-[(3-Bromophenyl)amino]-3-cyano-6-quinoliny]-4-(bis-(2-methoxyethyl)amino)-2-butynamide

Isobutyl chloroformate (0.785g, 5.75mmol) was dropwise added into an ice cold solution of 4-(bis-methoxyethylamino)-2-butynoic acid (1.9g, 8.85mmol) and N-methylmorpholine (0.9386g, 9.28mmol) in 50mL of tetrahydrofuran under N₂. After stirring for 30min, a solution of 1.5g (4.42mmol) of 6-amino-4-[(3-bromophenyl)amino]-quinoline-3-carbonitrile in 10mL of pyridine was added dropwise and the mixture was stirred at 0°C for 2hr. The reaction was quenched with ice water, poured into saturated sodium bicarbonate and brine, and extracted with ethyl acetate. The ethyl acetate layer was concentrated and purified by flash column chromatography. The product fractions were collected, and dried in vacuo to give 0.82 (35%) of light brown solid; ESMS m/z 536.1, 538.1 (M+H⁺); mp 98-101°C.

Example 76

N-[4-[(3-Bromophenyl)amino]-3-cyano-6-quinoliny]-4-(N-methoxyethyl-N-methylamino)-2-butynamide

Isobutyl chloroformate (0.785g, 5.75mmol) was dropwise added into an ice cold solution of 4-(N-methoxyethyl-N-methylamino)-2-butynoic acid (1.5g, 8.84mmol) and N-methylmorpholine (1.36g, 13.3mmol) in 60mL of tetrahydrofuran under N₂. After stirring for 30min, a solution of 1.5g (4.42mmol) of 6-amino-4-[(3-bromophenyl)amino]-quinoline-3-carbonitrile in 15mL of pyridine was added dropwise and the mixture was stirred at 0°C for 2hr. The reaction was quenched with ice water, poured into saturated sodium bicarbonate and brine, and extracted with ethyl acetate. The ethyl acetate layer was concentrated and purified by flash column chromatography. The product fractions were collected, and dried in vacuo to give 0.32 (15%) of reddish brown solid; ESMS m/z 492.0, 494.0 (M+H⁺); mp 95°C (dec).

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Example 77

- 10 N-[4-[(3-Bromophenyl)amino]-3-cyano-6-quinolinyl]-4-(N-allyl-N-methylamino)-2-
 butynamide
- 15 Isobutyl chloroformate (0.785g, 5.75mmol) was dropwise added into an ice cold
 solution of 4-(N-allyl-N-methylamino)-2-butynoic acid (1.4g, 8.84mmol) and N-
 methylmorpholine (0.94g, 9.3mmol) in 80mL of tetrahydrofuran under N₂. After
 stirring for 30min, a solution of 1.5g (4.42mmol) of 6-amino-4-[(3-bromophenyl)-
 amino]-quinoline-3-carbonitrile in 15mL of pyridine was added dropwise and the
 mixture was stirred at 0°C for 2hr. The reaction was quenched with ice water, poured
 into saturated sodium bicarbonate and brine, and extracted with ethyl acetate. The
 ethyl acetate layer was concentrated and purified by flash column chromatography.
 The product fractions were collected, and dried in vacuo to give 0.60 (29%) of brown
 solid; ESMS m/z 474.4, 476.4 (M+H⁺); mp 133-135°C.

15 **Example 78**

- 30 1-Methyl-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid [4-(3-bromo-phenylamino)-3-
 cyano-quinolin-6-yl]-amide
- 35 To a solution of 1 g (2.95 mmol) of 6-amino-4-[(3-bromophenyl)amino]-quinoline-3-
 carbonitrile and 1.9 g (14.7 mmol) of diisopropylethylamine was stirred in 19 ml of
 tetrahydrofuran and solid N-methyl-1,2,5,6-tetrahydronicotinyl chloride
 hydrochloride was added portionwise at 0°C. After stirring 1 hr at 0°C and 2 hr at
 room temperature, the mixture was poured into saturated sodium bicarbonate and
 extracted with ethylacetate. The solution was dried over magnesium sulfate. Solvent
 was removed and the residue was recrystallized from methanol-ethylacetate giving
 0.92 g of a yellow powder : mass spectrum (electrospray, m/e,): M+H 462.4, 464.4.

45 **Example 79**

- 45 4-((2S)-2-Methoxymethylpyrrolidin-1-yl)but-2-ynoic Acid [4-(3-
 bromophenylamino)-3-cyanoquinolin-6-yl]-amide
- 50 To an ice cold solution of 1.46 g (7.40 mmol) of 4-((2S)-2-methoxymethylpyrrolidin-
 1-yl)but-2-ynoic acid in 85 mL of THF under N₂ was added 0.897 g (8.88 mmol) of

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N-methylmorpholine and 0.811 g (5.92 mmol) of isobutyl chloroformate. After stirring in the cold for 30 min, a solution of 1.00 g (2.96 mmol) of 6-amino-4-[(3-bromophenyl)amino]-quinoline-3-carbonitrile in 8 mL of pyridine was added dropwise. The reaction was slowly warmed to 25°C over 3 h. The reaction was poured into ice water, satd NaHCO₃ was added and the product was extracted with ethyl acetate. After drying and solvent evaporation, the residue was chromatographed on silica gel (10% methanol in ethyl acetate). The yield was 0.560 g of 4-((2S)-2-methoxymethylpyrrolidinyl-1-yl)but-2-yneic acid [4-(3-bromophenylamino)-3-cyanoquinolin-6-yl]amide as a brown foam: mass spectrum (electrospray, m/e):

10 M+H 518.0, 520.0.

Example 80
4-((2S)-2-methoxymethylpyrrolidin-1-yl)butynoic Acid
n-Butyllithium solution in hexane (35.9 mmol) was added over 10 min to a solution of 5.49 g (35.9 mmol) of (2S)-2-methoxymethyl-1-prop-2-vnylpyrrolidine in 100 mL of THF at -78°C under N₂. After stirring cold for 1 h, CO₂ was bubbled into the solution as it slowly came to 25°C. After stirring overnight, 100 mL of water was added, the reaction was extracted with ethyl acetate and the extracts were discarded. The reaction was adjusted to pH 7 with 20% H₂SO₄ and solvent was removed. The residue was slurried with methanol and filtered. The filtrate was evaporated and dried in vacuo to give 7.06 g of 4-((2S)-2-methoxymethylpyrrolidin-1-yl)butynoic acid as a brown foam: mass spectrum (electrospray, m/e): M+H 198.0.

Example 81
(2S)-2-Methoxymethyl-1-prop-2-vnylpyrrolidine
A mixture of 4.82 g (41.9 mmol) of S-2-(methoxymethyl)pyrrolidine, 13.7 g (41.9 mmol) of cesium carbonate and 5.00 g (41.9 mmol) of propargyl bromide in 80 mL of acetone was stirred at 25°C overnight. The reaction was filtered and solvent was removed from the filtrate. The residue was diluted with a small amount of water and satd NaHCO₃ and extracted with ether. The extract was treated with Darco, dried and

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10 evaporated to give 5.93 g of (2S)-2-methoxymethyl-1-prop-2-ynylpyrrolidine as a yellow orange oil: mass spectrum (electrospray, m/e): 153.8.

Example 82

15 **5 4-(1,4-Dioxa-8-azaspiro[4,5]dec-8-yl)but-2-yneic Acid [4-(3-Bromophenylamino)-3-**

cyanooquinolin-6-yl] Amide

20 To an ice cold solution of 1.75 g (7.78 mmol) of 4-(1,4-dioxa-8-azaspiro[4,5]dec-8-yl)but-2-yneic acid in 100 mL of THF under N₂ was added 0.942 g (9.33 mmol) of N-methylmorpholine followed by 0.852 g (6.22 mmol) of isobutyl chloroformate.

25 10 After stirring in the cold for 30 min, a solution of 1.05 g (3.11 mmol) of 6-amino-4-[(3-bromophenyl)amino]-quinoline-3-carbonitrile in 8 mL of pyridine was added dropwise. After stirring in the cold for 5 h, the reaction was poured into ice water and said NaHCO₃ was added. The mixture was extracted with ethyl acetate and the extracts were dried and evaporated. Chromatography of the residue on silica gel

30 15 (20% methanol in ethyl acetate) gave 0.590 g of 4-(1,4-dioxa-8-azaspiro[4,5]dec-8-yl)but-2-yneic acid [4-(3-bromophenylamino)-3-cyanoquinolin-6-yl] amide as a brown foam: mass spectrum (electrospray, m/e): M+H 546.0, 548.1.

Example 83

35 20 **4-(1,4-Dioxa-8-azaspiro[4,5]dec-8-yl)but-2-yneic Acid**

n-Butyllithium in hexane (55.8 mmol) was added dropwise to a solution of 10.1 g (55.8 mmol) of 3-(1,4-dioxa-8-azaspiro[4,5]dec-8-yl)but-2-yne in 185 mL of THF at -78°C under N₂. After stirring at -78°C for 1 h, CO₂ was bubbled into the solution as it slowly came to 25°C . After stirring overnight, the reaction was diluted with 150 mL of water , extracted with ethyl acetate and the extracts were discarded. The solution was adjusted to pH 6 with 2 M sulfuric acid and evaporated. The residue was slurried with methanol and filtered. The filtrate was evaporated and dried in vacuo to give 4.5 g of 4-(1,4-dioxa-8-azaspiro[4,5]dec-8-yl)but-2-yneic acid as a brown amorphous solid: mass spectrum electrospray, m/e): M+H 225.8.

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Example 84**3-(1,4-Dioxa-8-azaspiro[4,5]dec-8-yl)but-2-yne**

A mixture of 10.0 g (69.9 mmol) of 1,4-dioxa-8-azaspiro[4,5]decane, 22.8 g (69.9 mmol) of cesium carbonate and 8.32 g (69.9 mmol) of propargyl bromide in 165 mL of acetone was stirred overnight at 25 °C. The reaction was filtered and the filtrate was evaporated to dryness. A small amount of water and satd NaHCO₃ was added to the residue and it was extracted with ether. The ethereal extracts were treated with Darco, dried and evaporated to give 10.8 g of 3-(1,4-dioxa-8-azaspiro[4,5]dec-8-yl)but-2-yne as a yellow orange oil: mass spectrum (electrospray, m/e): M+H 181.8.

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Example 85**4-(3-Bromo-phenylamino)-6-(2-ethoxy-3,4-dioxo-cyclobut-1-enylamino)-quinoline-3-carbonitrile**

A mixture of 1.00 g (2.95 mmol) 6-amino-4-(3-chloro-phenylamino)-quinoline-3-carbonitrile, 20 mL ethanol, and 0.873 mL (5.90 mmol) 3,4-diethoxy-3-cyclobutene-1,2-dione was heated to reflux under N₂. At 4 hours removed heat, cooled to 25°C and stirred overnight. Decanted off solution and stripped solvent. Added ether to crystallize, collected solids and dried. Boiled in ethyl acetate to remove cyclobutene starting material. Dried in vacuo, giving 249 mg of yellow solid: mass spectrum (electrospray m/e): M+H = 463.2.

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Example 86**4-(4-Chloro-2-fluoro-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile**

A mixture of 2.0 g of 4-chloro-6,7-dimethoxy-quinoline-3-carbonitrile, 1.46 g of 4-chloro-2-fluoroaniline, 0.925 g of pyridine hydrochloride, and 125 ml of ethoxyethanol was stirred under nitrogen, at reflux temperature for 1 h. The mixture was cooled and added to 1000 ml of water. To this mixture was added sodium carbonate to pH 9. The product was collected, washed with water, and dried to give 2.61 g of 4-(4-chloro-2-fluoro-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile as a solid, mp 139-141°C; mass spectrum (electrospray, m/e): M+H 357.9.

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Example 874-(4-Chloro-2-fluoro-phenylamino)-6,7-dihydroxy-quinoline-3-carbonitrile

- 15 A mixture of 0.358 g of 4-(4-chloro-2-fluoro-phenylamino)-6,7-dimethoxy-
5 quinoline-3-carbonitrile and 3 g of pyridine hydrochloride was stirred under nitrogen
at 210 -220°C for 20 minutes. The mixture was cooled and added to 50 ml of 3%
ammonium hydroxide solution. The product was collected, washed with water, and
dried to give 0.302 g of 4-(4-chloro-2-fluoro-phenylamino)-6,7-dihydroxy-quinoline-
20 3-carbonitrile as a solid, mp 270-272°C; mass spectrum (EI, m/e): M 329.0363.

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Example 884-(4-Chloro-2-fluoro-phenylamino)-6-methoxy-7-(2-pyridin-4-yl-ethoxy)-quinoline-
3-carbonitrile

- 25 To a solution of 0.655 g of triphenylphosphine in 20 ml of tetrahydrofuran was added
15 dropwise 0.348 mg of diethyl azodicarboxylate. The solution was stirred for one
30 minute and added to a mixture of 0.330 g of 4-(4-chloro-2-fluoro-phenylamino)-6,7-
dihydroxy-quinoline-3-carbonitrile and 0.500 g of 2-(4-pyridyl)ethanol in 100 ml of
tetrahydrofuran. The mixture was stirred at room temperature for 4 hours, and 10 ml
of methanol was added.
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20 To a solution of 0.655 g of triphenylphosphine in 20 ml of tetrahydrofuran was added
dropwise 0.348 mg of diethyl azodicarboxylate. The solution was stirred for one
40 minute and added to the above mixture. The mixture was stirred overnight and
concentrated in vacuo. The residue was chromatographed on silica gel eluting with
5% methanol in dichloromethane. Solvent was removed from product fractions
45 giving 0.034 g of 4-(4-Chloro-2-fluoro-phenylamino)-6-methoxy-7-(2-pyridin-4-yl-
ethoxy)-quinoline-3-carbonitrile as a white wax; mass spectrum (EI, m/e): M
448.1104. The regiochemistry was assigned unequivocally by NMR analysis (Proton,
DQF-COSY, NOESY, ^1H - ^{13}C)-HMQC, ^1H - ^{13}C)-HMBC, ^1H - ^{15}N)-HMBC.

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Example 89

- 10 4-[*(2-Methoxy-ethyl)-methyl-amino*]-but-2-enoic acid [*4-(3-chloro-4-fluoro-*
phenylamino)*-3-cyano-7-methoxy-quinolin-6-yl*-amide dihydrochloride
- 15 To a stirring solution of 1.2 g (3.5 mmol) of 6-amino-4-(3-chloro-4-fluoro-
5 phenylamino)-7-methoxy-quinoline-3-carbonitrile and 0.52 g (4.0 mmol) of
diisopropylethylamine in 40 ml of tetrahydrofuran at 0°C was added a solution of 4-
bromo crotonyl chloride in 10 ml of tetrahydrofuran. After 45 min, 1.87 (21 mmol) of
20 2-methoxyethyl methyl amine was added. After 1hr at room temperature, the
mixture was poured into a solution of sodium bicarbonate and extracted with ethyl
acetate. The organic solution was dried over magnesium sulfate. The solvent was
removed and the residue was purified by chromatography on silica gel. Product eluted
25 with ethyl acetate-methanol-triethylamine 40:8:1 giving 0.87 g of the free base. This
was dissolved in 20 ml of ethyl acetate and 10 ml of a solution of hydrogen chloride
in ether was added. The solid was collected giving 1.02 g of the title compound a a
30 yellow powder: mass spectrum (electrospray, m/e): M+H 498.0, (M+2H)² 248.5.

Example 90

- 35 (S)-4-(*2-Methoxymethyl-pyrrolidin-1-yl*)-but-2-enoic acid [*4-(3-chloro-4- fluoro-*
phenylamino)*-3-cyano-7-methoxy-quinolin-6-yl*-amide dihydrochloride
- 40 20 By using the method of Example 89, 1.2 g (3.5 mmol) of 6-amino-4-(3-chloro-4-
fluoro-phenylamino)-7-methoxy-quinoline-3-carbonitrile and 2.4 g (21 mmol) of
(S)-(+)-2-(methoxymethyl) pyrrolidine were converted to 1.5 g the title compound,
obtained as a yellow powder: mass spectrum (electrospray, m/e): M+H 524.0,
(M+2H)² 262.4. This reaction can also be done with (R)-(-)-2-(methoxymethyl)
- 45 25 pyrrolidine or racemic 2-(methoxymethyl) pyrrolidine giving the R-enantiomer or the
racemate, respectively.

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Example 91

- 10 4-(3-Hydroxymethyl-piperidin-1-yl)-but-2-enoic acid [4-(3-chloro-4-fluoro-
phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide hydrochloride

15 By using the method of Example 89, 1.1 g (3.2 mmol) of 6-amino-4-(3-chloro-4-fluoro-phenylamino)-7-methoxy-quinoline-3-carbonitrile and 2.2 g (19.2 mmol) of 3-hydroxymethyl-piperidine were converted to 0.76 g the title compound, obtained as a yellow powder: mass spectrum (electrospray, m/e): M+H 524.0, (M+2H)² 262.3.

20 **Example 92**

- 10 4-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide

25 By using the method of Example 89, 1.05 g (3.06 mmol) of 6-amino-4-(3-chloro-4-fluoro-phenylamino)-7-methoxy-quinoline-3-carbonitrile and 2.6 g (18.4 mmol) of 1,4-dioxa-8-azaspiro[4.5]decane were converted to 0.62 g the title compound. The free base obtained as a yellow foam: mass spectrum (electrospray, m/e): M+H 552.0, (M+2H)² 270.5.

30 **Example 93**

- 35 4-(2-Hydroxymethyl-piperidin-1-yl)-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide

40 By using the method of Example 89, 1.05 g (3.06 mmol) of 6-amino-4-(3-chloro-4-fluoro-phenylamino)-7-methoxy-quinoline-3-carbonitrile and 2.1 g (18.4 mmol) of 2-hydroxymethyl-piperidine were converted to 0.67 g the title compound. The free base was obtained as an off-white powder: mass spectrum (electrospray, m/e): M+H 524.3, (M+2H)² 267.7.

45 **Example 94**

- 45 4-Bromo-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide.

50 30 By using the method of Example 15, 4-bromo crotonyl chloride and 6-amino-4-(3-chloro-4-fluoro-phenylamino)-7-methoxy-quinoline-3-carbonitrile was converted to

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10 the title compound which was obtained as a solid that could be purified with boiling methanol.

Example 95

15 3-[3-[4-(3-Chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-ylcarbamoyl]-allyl}-5-methyl-thiazol-3-ium bromide

A solution of 0.5 g (1 mmol) of 4-bromo-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide and 0.6 g (6.1 mmol) of 5-methyl thiazole was refluxed for 4 hr. The mixture was diluted with ethyl acetate and cooled. Solid was collected and recrystallized from methanol-acetone-ethyl acetate to give 0.2 g of the title compound as a yellow powder: mass spectrum (electrospray, m/e): M⁺ 508.0, 509.9, (M+H)² 254.4, 255.1.

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Example 96

15 3-[3-[4-(3-Chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-ylcarbamoyl]-allyl}-4-methyl-thiazol-3-ium bromide

A solution of 0.7 g (1.4 mmol) of 4-bromo-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide and 0.85 g (8.6 mmol) of 4-methyl thiazole was refluxed for 17 hr. The mixture was diluted with ethyl acetate and cooled. Solid was collected and recrystallized from methanol-acetone-ethyl acetate to give 0.3 g of the title compound as a yellow powder: mass spectrum (electrospray, m/e): M⁺ 507.9, 509.8, (M+H)² 254.4, 255.1.

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Example 97

25 Methyl 4-benzyloxy-2-(dimethylaminomethyleneamino)-5-methoxybenzoate

A stirred mixture of 70.0g (244 mmol) of methyl 2-amino-4-benzyloxy-5-methoxybenzoate (*Phytochemistry* 1976, 15, 1095) and 52 ml of dimethylformamide dimethyl acetal was heated at 100°C for 1.5 h, cooled, and evaporated directly under high vacuum to give 81.3 g of off-white solid, mp 134-140°C; NMR (CDCl₃) δ 3.01 (s, Me₂N).

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Example 98

- 10 7-benzyloxy-4-hydroxy-6-methoxy-quinoline-3-carbonitrile
- To a stirred solution of 26.9 ml of *n*-butyllithium (2.5 M in hexane) in 50 ml of THF at -78°C was added a 3.51 ml of acetonitrile in 20 ml of THF during 10 min. After 5 stirring at -78°C for 30 min, the mixture was treated with 10 g of methyl 4-benzyloxy-2-(dimethylaminomethyleneamino)-5-methoxybenzoate in 20 ml of THF during 5 min. After 15 min at -78°C the stirred mixture was warmed to 0°C for a further 30 min. It was then treated with 5 ml of acetic acid, warmed to 25°C and 20 stirred for 30 min. The mixture was evaporated to dryness, and diluted with aqueous 10 sodium bicarbonate. The resulting off-white solid was filtered, washed with water, ethyl acetate and ether. After drying, 4.5 g of 7-benzyloxy-4-hydroxy-6-methoxy-25 quinoline-3-carbonitrile was obtained as an off-white solid, dec > 255°C ; mass spectrum (electrospray, m/e) M+H 307.

15 **Example 99**

- 30 7-benzyloxy-4-chloro-6-methoxy-quinoline-3-carbonitrile
- To a stirred suspension of 1 g of 7-benzyloxy-4-hydroxy-6-methoxy-quinoline-3-carbonitrile in 10 ml of methylene chloride was added 5 ml of oxalyl chloride (2M in 35 methylene chloride), and 2 drops of N,N-dimethylformamide. The mixture was 20 refluxed for 20 min and to it was slowly added aqueous sodium bicarbonate until the bubbling ceased. Following separation of the layers, the organic layer was evaporated to a small volume, then passed through a plug of magnesol. Elution with 50 ml 40 methylene chloride, followed by evaporation provided 0.6 g of 7-benzyloxy-4-chloro-6-methoxy-quinoline-3-carbonitrile as a pale yellow solid, mp 282-284°C; 25 mass spectrum (electrospray, m/e) M+H 325.

45 **Example 100**

4-chloro-7-hydroxy-6-methoxy-quinoline-3-carbonitrile

- A stirred suspension of 0.54 g of 7-benzyloxy-4-chloro-6-methoxy-quinoline-3-carbonitrile in 10 ml of methylene chloride was cooled to 0°C. To this was added 10 50 ml of boron trichloride (1M in methylene chloride). The mixture darkened as it

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warmed to room temperature and a solid precipitated out. After stirring for 1 hour, no further reaction was observed. The solid (unreacted starting material) was filtered off, the remaining solution was cooled to 0°C and quenched by the dropwise addition of methanol. Following evaporation of the solvent, the residue was dissolved in methylene chloride/methanol/acetone. Purification of this residue was carried out using silica gel chromatography, eluting with a solvent gradient of 1 to 5 percent methanol/methylene chloride, to provide 0.075 g of 4-chloro-7-hydroxy-6-methoxy-quinoline-3-carbonitrile as a yellow solid, dec >245°C; mass spectrum (electrospray, m/e) M+H 235.2.

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Example 101**4-chloro-6-methoxy-7-(3-pyridin-4-yl-propoxy)-quinoline-3-carbonitrile**

A mixture of 0.070 g of 4-chloro-7-hydroxy-6-methoxy-quinoline-3-carbonitrile, 0.062 g of 3-(4-pyridyl)-1-propanol and 0.235 g of triphenylphosphine in 3 ml of methylene chloride under nitrogen was cooled to 0°C. To this was added 0.14 ml of diethyl azodicarboxylate dropwise. After 30 minutes, the reaction mixture was warmed to room temperature and further stirred for 2 hours. The mixture was concentrated down to 1ml and purified by silica gel chromatography, eluting with a solvent gradient of 1 to 2 percent methanol/methylene chloride, to provide 0.090 g of 4-chloro-6-methoxy-7-(3-pyridin-4-yl-propoxy)-quinoline-3-carbonitrile as an off-white gum.

Example 102**4-(3-hydroxy-4-methyl-phenylamino)-6-methoxy-7-(3-pyridin-4-yl-propoxy)-quinoline-3-carbonitrile**

A mixture of 0.090 g of 4-chloro-6-methoxy-7-(3-pyridin-4-yl-propoxy)-quinoline-3-carbonitrile, 0.050 g of 3-hydroxy-4-methylaniline, 0.039 g of pyridine hydrochloride and 3 ml of ethoxyethanol was stirred under nitrogen at reflux temperature for 20 minutes. The mixture was cooled and filtered. The product was washed with saturated sodium bicarbonate, water, then dried to give 0.080 g of 4-(3-hydroxy-4-methyl-phenylamino)-6-methoxy-7-(3-pyridin-4-yl-propoxy)-quinoline-3-carbonitrile

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hydrochloride as a solid, dec >153°C ; mass spectrum (electrospray, m/e): M+H
10 440.9.

Example 103

5 **4-Diallylamino-but-2-enoic acid**

[4-(3-chloro-4-fluoro-phenylamino)-3cyano-7-methoxy-quinolin-6-yl]-amide

A solution of 0.24 g (0.5mmol) of 4-bromo-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide in 1 ml of N,N-dimethyl-formamide and 4 ml of tetrahydrofuran was stirred with 0.49 ml (4 mmol) of

20 diallylamine for 3 hr. The reaction was quenched with 10 ml of saturated sodium bicarbonate and 10 ml of ethyl acetate. The insoluble precipitate was collected and washed with water to give 23.7 mg of the title compound (free base); mass spectrum (electrospray, m/e): M+H 506.0. The ethyl acetate layer was washed with water.

25 After the solvent was removed, the crude product was purified by preparative HPLC (C18 column, Gradient from 2% acetonitrile containing 0.05% trifluoroacetic acid to 100% acetonitrile containing 0.05% trifluoroacetic acid in 12 min) to yield 97.9 mg of the product as the bis-trifluoroacetate salt ; mass spectrum (electrospray, m/e):
30 M+H 506.0.

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35 20 **Example 104**

4-[Bis-(2-methoxy-ethyl)-amino]- but-2-enoic acid

[4-(3-chloro-4-fluoro-phenylamino)- 3-cyano-7-methoxy-quinolin-6-yl]-amide

In the manner of Example 103, 4-bromo-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide and bis-(2-methoxyethyl)-amine was converted to 52.3 mg of the title compound as the bis-trifluoroacetate salt
40 mass spectrum (electrospray, m/e): M+H 542.0.

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Example 105**4-([1,3]Dioxolan-2-ylmethyl-methyl-amino)-but-2-enoic acid
3-cyano-7-methoxy-quinolin-6-yl]-amide**

In the manner of Example 103, 4-bromo-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide and [1,3]dioxolan-2-yl-methyl-methyl-amino was converted to 116.2 mg of the title compound as the bis-trifluoroacetate salt; mass spectrum (electrospray, m/e): M+H 526.0.

Example 106**4-[Bis-(2-hydroxy-ethyl)-amino]-but-2-enoic acid
[4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide**

In the manner of Example 103, 4-bromo-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide and bis-(2-hydroxy-ethyl) amine was converted to 22.2 mg of the title compound (free base), mass spectrum (electrospray, m/e): M+H 514.0 and 60.7 mg of the title compound as the bis-trifluoroacetate salt; mass spectrum (electrospray, m/e): M+H 514.0.

Example 107**4-Thiomorpholin-4-yl-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide**

In the manner of Example 103, 4-bromo-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide and thiomorpholine was converted to 48.1 mg of the title compound (free base), mass spectrum (electrospray, m/e): M+H 512.0 and 33.2 mg of the title compound as the bis-trifluoroacetate salt; mass spectrum (electrospray, m/e): M+H 512.0.

Example 108**4-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-but-2-enoic acid****[4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide**

In the manner of Example 103, 4-bromo-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide and 4-(2-hydroxy-ethyl)

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10 piperazine was converted to 32.3 mg of the title compound (free base) and mass spectrum (electrospray, m/e): M+H 539.1, 42.2 mg of the title compound as the bis-trifluoroacetate salt); mass spectrum (electrospray, m/e): M+H 539.1.

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Example 109**4-(1,4,7-Trioxa-10-aza-cyclododec-10-yl)-but-2-enoic acid****[4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide**

20 In the manner of Example 103, 4-bromo-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide and 1,4,7-trioxa-10-aza cyclododecane was converted to 37.5 mg of the title compound(free base) and mass spectrum (electrospray, m/e): M+H 584.1, 17.1 mg of the title compound as the bis-trifluoroacetate salt); mass spectrum (electrospray, m/e): M+H 584.1.

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Example 110**15 4-(Methoxy-methyl-amino)-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide**

30 A mixture of 1g of the 4-bromo-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide (2.04 mmol, 1 equiv.), 1.2g of N,O-Dimethylhydroxylamine hydrochloride (12.25 mmol, 9 equiv.), and 1.5g of 35 sodium bicarbonate (18.38 mmol, 9 equiv.) in DMF (10ml) was stirred at room temperature for 24 hours. Ethyl acetate was added to the reaction mixture, and the crude product was filtered. After flash chromatography (ethyl acetate:methanol:triethylamine 40:4:1), 0.486 g of the title compound was isolated (50.7% yield); mp 210-217 °C.

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Example 111**45 4-(4-Hydroxy-piperidin-1-yl)-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide**

50 A mixture of 250 mg (0.51 mmol) of the 4-bromo-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide, and 103.2 mg (1.02 mmol) of 4-hydroxypiperidine in 2.25 ml dimethylformamide was stirred at room

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10 temperature for 3 hr. Saturated sodium bicarbonate was added and the precipitate was filtered and washed with hexane to give the first crop of product. The filtrate was extracted with ethyl acetate and the organic layer purified by preparative TLC to yield the second crop. The two crops were combined to give 105.8 mg (41%)
15 tan solid: mp >215°C.

Example 112

20 4-[1,4']Bipiperidinyl-1'-yl-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-
cyano-7-methoxy-quinolin-6-yl]-amide

25 10 A mixture of 250 mg (0.51 mmol) of 4-bromo-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide, and 172 mg (1.02 mmol) of 4-piperidinopiperidine in 5.0 ml dimethylformamide was stirred at room temperature for 4 hr and at 60°C for 1 hr. After the mixture was cooled, the suspension was diluted with saturated sodium bicarbonate solution and extracted with
30 15 ethyl acetate. The extracts were evaporated to an oil and purified by preparative TLC to yield 100 mg (40%) yellow solid: mp 140-144°C.

Example 113

35 20 4-Thiazolidin-3-yl-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-
methoxy-quinolin-6-yl]-amide

40 40 A mixture of 250 mg (0.51 mmol) of 4-bromo-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide, and 80µL (1.02 mmol) of thiazolidine in 2.25 ml dimethylformamide was stirred at room temperature for 19.5 hr. After the mixture was cooled, the suspension was diluted with saturated
45 25 sodium bicarbonate solution and extracted with ethyl acetate. The extracts were evaporated to an oil and purified by preparative TLC to yield 95.6 mg (38%) yellow solid: mp 135-138°C.

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Example 114**4-(2,6-Dimethyl-piperidin-1-yl)-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide**

A mixture of 250 mg (0.51 mmol) of 4-bromo-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide, and 137 μ L (1.02 mmol) of cis-2,6-dimethylpiperidine in 2.25 ml dimethylformamide was stirred at room temperature for 3 hr. The reaction mixture was diluted with saturated sodium bicarbonate solution and extracted with ethyl acetate. The extracts were evaporated to an oil, washed with hexane and dried under reduced pressure to yield 170.4 mg (64%) tan solid: mp 120-122°C.

Example 115**4-[Bis-(2-hydroxy-propyl)-amino]-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide**

A mixture of 250 mg (0.51 mmol) of 4-bromo-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide, and 136 mg (1.02 mmol) of 1,1'-iminodi-2-propanol in 2.25 ml dimethylformamide was stirred at room temperature for 3 hr and at 60°C for 2 hr. After the mixture was cooled, saturated sodium bicarbonate solution was added and the solution was subsequently extracted with ethyl acetate. The extracts were evaporated to an oil, washed with hexane and dried under reduced pressure. Yield 240.1 mg (87%) tan solid: mp 122-125°C.

Example 116**4-(3-Hydroxy-pyrrolidin-1-yl)-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide**

A mixture of 250 mg (0.51 mmol) of 4-bromo-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide, and 85 μ L (1.02 mmol) of R-(+)-3-pyrrolidinol in 5.0 ml dimethylformamide was stirred at room temperature for 4 hr and at 60°C for 1 hr. After the mixture was cooled, saturated sodium bicarbonate solution was added and the solution was subsequently extracted

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10 with ethyl acetate. The extracts were evaporated to an oil, and purified by preparative TLC. Yield 84.2 mg (33%) yellow solid: mp 215-220°C.

Example 117

15 4-[2-Hydroxy-ethyl]-methyl-amino-but-2-enoic acid [4-(3-chloro-4-fluoro-
phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide
20 4-bromo-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-
methoxy-quinolin-6-yl]-amide (250mg,.51mmol.) and 2-(methylamino)-ethanol(97
25 mg,1.02mmol.) were dissolved with stirring, under nitrogen, in 9 ml anhydrous
10 dimethylformamide. After 48 hours, the mixture was partitioned between saturated
sodium bicarbonate solution, and ethyl acetate. The organic phase was separated,
dried over magnesium sulfate, filtered, and evaporated to give a gum. It was
chromatographed on silica gel, and eluted with 40/4/1 (ethyl acetate/methanol/tri-
ethylamine) producing 183 mg (74%) of the purified product as a yellow solid: mp
15 210-214°C.

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Example 118

35 4-(2,5-Dimethyl-pyrrolidin-1-yl)-but-2-enoic acid [4-(3-chloro-4-fluoro-
phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide
20 In the same manner as Example 117, 4-bromo-but-2-enoic acid [4-(3-chloro-4-
fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide. (.51mmol.) was
40 reacted with 2,5-dimethylpyrrolidine (1.02mmol.,101mg.) in dimethylformamide. The
crude product was also purified via chromatography as Example 117, leaving 214mg.
(82%) of the yellow product: mp 110-113°C.

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Example 119

45 4-(4,4-Dihydroxy-piperidin-1-yl)-but-2-enoic acid [4-(3-chloro-4-fluoro-
phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide
50 After the procedure of Example 117, 4-bromo-but-2-enoic acid [4-(3-chloro-4-fluoro-
phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide(.51mmol.) was stirred in
30 dimethylformamide with 4-piperidone monohydrate hydrochloride (470 mg.,

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10 3.06mmol.), and sodium bicarbonate (386mg.,4.59mmol.), for 24 hours. The crude product was purified in the same manner as Example 117 and produced 192 mg. (72%) of the product as a yellow solid: mp 225-30°C.

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Example 1206-(4-Chlorobutylamino)-4-(3-chloro-4-fluorophenylamino)-7-methoxy -3-quinolinecarbonitrile

20 To a solution of 1.12 g of 4-chlorobutanal and 5.3 ml of 3M sulfuric acid in 11 ml of tetrahydrofuran, at 0°C, was added an solution of 2.0 g of 6-amino-4-(3-chloro-4-
10 fluoro-phenylamino)-7- methoxy -3-quinolinecarbonitrile in 40 ml of dimethylformamide. To this was added portionwise 0.4 g of sodium borohydride. After
25 I hr another 1.0 g of aldehyde , 10 ml of dimethylformamide, and 5 ml of 3M sulfuric acid was added followed by the portionwise addition of 0.8 g of sodium borohydride.
After 2 hrs, the mixture was poured into water and the Ph was adjusted to 9. The
15 mixture was extracted with ethyl acetate several times. The organic solution was dried over magnesium sulfate and the solvent was removed giving the title compound as an oil which was used without additional purification.

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Example 12120 4-(3-Chloro-4-fluoro-phenylamino)-7-methoxy-6-(4-morpholin-4-yl-butylamino)-quinaline-3-carbonitrile

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Example 12225 4-(3-Chloro-4-fluoro-phenylamino)-7-methoxy-6-pyrrolidin-1-yl-quinoline-3-carbonitrile

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A mixture of 2.5 g of 6-(4-chlorobutylamino)-4-(3-chloro-4-fluorophenylamino)-7-methoxy -3-quinolinecarbonitrile, 7.54 g of morpholine, and 0.17 g of sodium iodide in 30 ml of dimethylformamide was stirred at 750°C for 7 hrs. The mixture was poured into dilute sodium bicarbonate and solid was collected. This material was dissolved in ethylacetate. The solution was dried over magnesium sulfate. The solvent was removed and the residue was chromatographed on silica gel using ethyl acetate-

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methanol-triethylamine mixtures. A more polar component (0.54 g) was 4-(3-chloro-4-fluoro-phenylamino)-7-methoxy-6-(4-morpholin-4-yl-butylamino)-quinoline-3-carbonitrile; a less polar component (0.28 g) is the compound of this invention, 4-(3-chloro-4-fluoro-phenylamino)-7-methoxy-6-pyrrolidin-1-yl-quinoline-3-carbonitrile, obtained as a yellow solid: mass spectrum electrospray, m/e): M+H 397.4.

Example 123

4-(3-Chloro-4-fluoroanilino)-7-methoxy-6-(1H-pyrrol-1-yl)-3-quinolinecarbonitrile

10 A dimethylformamide (4.5 ml) suspension of 6-amino-4-[(3-chloro-4-fluoroanilino)-7-methoxy-3-quinolinecarbonitrile (0.2 g, 0.5839 mmol), 2,5-dimethoxytetrahydrofuran (0.1 ml, 0.77 mmol) and 4-chloropyridinium chloride (0.05g, 0.333 mmol) was heated at 108 °C overnight. The reaction solution was mixed with saturated sodium bicarbonated solution, brine and ethyl acetate. The ethyl acetate layer was separated, filtered through silica gel, and dried up to give 119 mg of 4-(3-Chloro-4-fluoroanilino)-7-methoxy-6-(1H-pyrrol-1-yl)-3-quinolinecarbonitrile as a cream-colored solid, mp 192.5-193.5 °C: high resolution mass spectrometry (electrospray, m/e): M+H 393.0913.

35 20 **Example 124**

6-[(2-chloroethyl)amino]-4-(3-chloro-4-fluoroanilino)-7-methoxy-3-quinolinecarbonitrile

To a solution of 1 g of 6-amino-4-[(3-chloro-4-fluoroanilino)-7-methoxy-3-quinolinecarbonitrile (2.92 mmol) in 20 ml of dimethylformamide at 0 °C, was added 40 a solution of 50% aqueous chloroformaldehyde (0.75 ml, 5.84 mmol) and 3 M sulfuric acid (2.92 ml, 8.76 mmol) in 5.3 ml of tetrahydrofuran, followed by 45 portionwise addition of 1.1 g of sodium borohydride powder (29.68 mmol). After the reaction mixture was stirred overnight at room temperature, the precipitated product was collected and partitioned between ethyl acetate and 10 N sodium hydroxide 50 solution. The organic layer was washed with brine and dried over sodium sulfate. The solvent was removed to yield 0.7648 g of a yellow solid. After recrystallization

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from acetonitrile, 0.5831 g of bright needle crystals were obtained; mp 207.2-
10 207.8 °C; high resolution mass spectrometry (EI, m/e): 404.060.

The filtrate was treated with 10 N sodium hydroxide and ethyl acetate, and worked up
as above to afford additional 0.38 g of crude product.

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Example 125**6-(1-Aziridinyl)-4-(3-chloro-4-fluoroanilino)-7-methoxy-3-quinolinecarbonitrile**

To a solution of 0.202 g (0.5 mmol) of 6-[2-chloroethyl]amino]-4-(3-chloro-4-fluoroanilino)-7-methoxy-3-quinolinecarbonitrile in 4 ml of dimethylformamide,
20 10 were added 0.075 g of sodium iodide (0.5 mmol) and 0.069 g of potassium carbonate (0.5 mmol). After the reaction solution was heated at 75 °C overnight, it was decanted into cold saturated sodium bicarbonate solution. The organic layer was separated and dried over sodium sulfate. The solvent was removed to yield 0.19 g of a light brown solid. The crude product was washed with hexane to give 0.1g of a yellow solid, mp
25 15 197-199 °C; high resolution mass spectrometry (EI, m/e): M 368.0888.

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Example 126**1-(Dimethylaminomethyleneamino)-3-chlorobenzene**

A mixture of 3-chloroaniline (63.8 g, 0.50 mol) and dimethylformamide dimethyl
35 20 acetal (106 ml, 0.75 mol) was heated at 100° for 2 h and evaporated at 60° at 0.5 mm Hg to give 91.8 g amber oil; ms 183.0 (M+H)⁺.

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Example 127**1-(Dimethylaminomethyleneamino)-3-chloro-4-nitrobenzene**

25 To a stirred solution of 1-(dimethylaminomethyleneamino)-3-chlorobenzene (67.5 g, 0.37 mol) in 148 ml of gl HOAc was added 70% nitric acid (70 ml, 1.11 mol) during 45 15 m with cooling at 10°. To the resulting solution was added Ac₂O (222 ml, 2.58 mol) during 30 m with cooling to maintain 15-20°. The solution was heated to 65° during 20 m. The resulting exothermic reaction was moderated with cool water at 65-50 30 68° for 45 m and then the reaction was heated at 65° for 90 m. The reaction mixture was cooled to 10°, stirred with DCM, and quenched with ice and 10 N NaOH (850

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ml). The organic layer was separated, washed thoroughly with water, dried, filtered through Magnesol, and concentrated to give 62.2 g red gummy solid. Flash chromatography of the residue on silica gel with 20:4:1 DCM-EtOAc-MeOH gave an amber solid, mp 78-90°; ms 228.1 (M+H)*.

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Example 128**(E/Z)-2-Cyano-3-(3-chloro-4-nitrophenylamino)acrylic Acid, Ethyl Ester**

To a stirred mixture of 1-(dimethylaminomethyleneamino)-3-chloro-4-nitrobenzene (7.9 g, 35 mmol) and 17.4 ml of HOAc at 25° was added ethyl cyanoacetate (5.2 g, 46 mmol). The resulting mixture was refluxed for 1.5 h, cooled, and stirred in water for 45 m. The resulting amber solid was filtered off, washed with water followed by 5:1 hexane-EtOAc, and dried; mp 195-205°; ms 294.1(M-H).

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Example 129**1,4-Dihydroquinoline-7-chloro-6-nitro-4-oxo-3-carbonitrile**

A stirred mixture of (E/Z)-2-cyano-3-(3-chloro-4-nitrophenylamino)acrylic acid, ethyl ester (2.36 g, 8.0 mmol) and 240 ml of Dowtherm A was heated at 260°C for 2 h, cooled, diluted with hexane, and filtered. The tan solid thus obtained was digested with boiling EtOAc, filtered, and dried to give 1.47 g, mp 320-330° (dec); ms 248.1 (M-H)*.

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Example 130**4,7-Dichloro-6-nitro-3-quinolinecarbonitrile**

A stirred mixture of 1,4-dihydroquinoline-7-chloro-6-nitro-4-oxo-3-carbonitrile(14.7 g, 58.9 mmol) and 59 ml of phosphorous oxychloride was refluxed for 3 h. The phosphorous oxychloride was removed in vacuo, and the residue was stirred with methylene chloride at 0°C and treated with a slurry of ice and potassium carbonate. The mixture was filtered through Celite, and the organic layer of the filtrate was separated, washed with water, dried, and concentrated to give 10.7 g of tan solid. Recrystallization from hexane-DCM gave mp 143-153°; ms 266.7 (M-H)*.

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Example 131

- 10 4-(3-Chloro-4-fluoroanilino)-7-chloro-6-nitro-3-quinolinecarbonitrile
- A stirred mixture of 4,7-dichloro-6-nitro-3-quinolinecarbonitrile (10.7 g, 40 mmol), 3-chloro-4-fluoroaniline (7.0 g, 48 mmol), pyridine hydrochloride (4.6 g, 40 mmol),
15 and 200 ml of 2-propanol was heated to reflux temperature and maintained for 1 h. The 2-propanol was evaporated off, and the residue was stirred in water with potassium bicarbonate (pH~8). The resulting solid was filtered, washed with water and 5:1 hexane-DCM, and dried. Recrystallization from EtOH gave 11.3 g of yellow
20 solid, mp 259-263°; ms 377.1 (M+H)⁺.

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Example 132

- 25 4-(3-Chloro-4-fluoroanilino)-7-(4-methyl-1-piperazinyl)-6-nitro-3-quinolinecarbonitrile
- A stirred mixture of 4-(3-chloro-4-fluoroanilino)-7-chloro-6-nitro-3-quinoline-
15 carbonitrile (1.88 g, 5.0 mmol), N-methylpiperazine (5 ml, 45 mmol), and 10 ml of toluene was refluxed for 45 m, evaporated to remove volatile matter, and stirred in water with potassium carbonate (2.75 g). The resulting solid was filtered, washed with water, and dried to give 2.26 g. An acetone solution was passed onto a pad of
30 silica gel; elution with 50:2:1 acetone-MeOH-TEA and evaporation gave a red solid,
35 mp 240-246°; ms 441.2 (M+H)⁺, 221.2 (M+2H)⁺.
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Example 133

- 40 6-Amino-4-(3-chloro-4-fluoroanilino)-7-(4-methyl-1-piperazinyl)-3-quinolinecarbonitrile
- 45 25 In the manner of Example 23 4-(3-chloro-4-fluoroanilino)-7-(4-methyl-1-piperazinyl)-6-nitro-3-quinolinecarbonitrile was reduced with iron powder and acetic acid in MeOH to give the title compound as an amorphous solid; ms 411.2 (M+H)⁺, 206.2 (M+2H)⁺.

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Example 134**10 N-[4-(3-Chloro-4-fluoroanilino)-3-cyano-7-(4-methyl-1-piperazinyl)-6-quinolinyl]-2-
butynamide**

15 To a stirred solution of 2-butynoic acid (0.25 g, 3.0 mmol) in 1.5 ml of DCM at 0° was added DCC (0.21 g, 1.0 mmol). After 15 m the mixture was warmed to 25°, re-cooled to 0°, and treated with 6-amino-4-(3-chloro-4-fluoroanilino)-7-(4-methyl-1-piperazinyl)-3-quinolinecarbonitrile (0.21 g, 0.50 mmol) followed by 0.5 ml DCM rinse. The resulting mixture was stirred at 25° for 18 h and filtered to remove dicyclohexyl urea. The filtrate was partitioned with water which contained potassium carbonate (0.4 g, 3 mmol). The organic layer was washed with water, dried, and concentrated. The residue was passed as a solution in DCM onto a pad of silica gel. The product was eluted with 50:2:1 acetone-MeOH-TEA and concentrated to give 0.165 g amorphous solid; ms 477.2 (M+H)⁺, 239.1 (M+2H)⁻².

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15 Example 135**30 3-Chloro-N-[4-(3-chloro-4-fluoroanilino)-3-cyano-7-(4-morpholiny)-6-
quinolinyl]propanamide**

35 To a stirred solution of 3-chloropropionic acid (0.65 g, 6.0 mmol) in 3 ml of DCM at 0° was added DCC (0.41 g, 2.0 mmol). After 15 m the mixture was warmed to 25°, re-cooled to 0°, and treated with 6-amino-4-(3-chloro-4-fluoroanilino)-7-(4-morpholiny)-3-quinolinecarbonitrile (0.40 g, 1.0 mmol) followed by 1 ml DCM rinse. The resulting mixture was stirred at 25° for 20 h, diluted with DCM, and stirred with aqueous sodium bicarbonate. The mixture was filtered to remove dicyclohexyl urea. The organic layer of the filtrate was washed with water, dried, and concentrated. The residue was passed as a solution in DCM onto a pad of silica gel. The product was eluted with 25:25:2:1 DCM-EtOAc-MeOH-TEA and concentrated to give 0.38 g amorphous solid; ms 488.1(M+H)⁺.

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Example 136

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N-[4-(3-chloro-4-fluoroanilino)-3-cyano-7-(4-morpholinyl)-6-quinolinyl]acrylamide

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To a stirred solution of 3-chloro-N-[4-(3-chloro-4-fluoroanilino)-3-cyano-7-(4-morpholinyl)-6-quinolinyl]propanamide (0.30 g, 0.61 mmol) in 1.2 ml of THF at 0° was added 1.2 ml of 1.0 M KOtBu/tBuOH dropwise during 1 m. After 2 h at 0° the reaction was quenched with solid CO₂ and partitioned with DCM-water. The organic layer was washed with water, dried, and evaporated to give 0.28 g of the title compound as a white amorphous solid; ms 452.2 (M+H)⁺.

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10 By using the methods described in Examples 1-136 above and the methods described in the patent applications WO-9843960 and WO-9909016, the compounds of this invention listed in Table 6 were prepared.

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Table 6

Example	Compound	m.p. (°C)	mass spectrum
137	4-[(2-Methoxy-ethyl)-methyl-amino]-but-2-enioic acid [4-(3-bromo-phenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]-amide	amorphous	538.0(M+H)
138	4-(2,4-Dichloro-5-methoxy-phenylamino)-7-[3-(4-hydroxypiperidin-1-yl)-propoxy]-6-methoxy-quinoline-3-carbonitrile	122-125	531.0(M+H)
139	4-(2,4-Dichloro-5-methoxy-phenylamino)-7-[3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propoxy]-6-methoxy-quinoline-3-carbonitrile	133-137	560.1 (M+H)
140	4-(2-Bromo-4-chloro-phenylamino)-7-{2-[(2-hydroxy-ethyl)-methyl-amino]-ethoxy}-6-methoxy-quinoline-3-carbonitrile	186-188	597.0 (M+H), 254.2 (M+2H) ¹²
141	4-(2,4-Dichloro-5-methoxy-phenylamino)-7-[3-[(2-hydroxy-ethyl)-methyl-amino]-propoxy]-6-methoxy-quinoline-3-carbonitrile	129-131	533.0 (M+H)
142	4-(2,4-Dichloro-5-methoxy-phenylamino)-6-methoxy-7-(3-thiomorpholin-4-yl-propoxy)-quinoline-3-carbonitrile	116-118	505.2(M+H)
143	4-(2,4-Dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(2-methoxy-ethylamino)-propoxy]-quinoline-3-carbonitrile	98-102	529.2 (M+H)
144	4-(2,4-Dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperidin-1-yl)-propoxy]-quinoline-3-carbonitrile	114-117	587.2 (M+H)
145	4-(2,4-Dichloro-5-methoxy-phenylamino)-7-[3-(2,6-dimethyl-morpholin-4-yl)-propoxy]-6-methoxy-quinoline-3-carbonitrile	155-157	545.3 (M+H)
146	4-(2-Bromo-4-chloro-phenylamino)-7-{2-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-ethoxy}-6-methoxy-quinoline-3-carbonitrile	156-158	562.1 (M+H), 281.7 (M+2H) ¹²
147	4-(2-Bromo-4-chloro-phenylamino)-7-[2-(4-hydroxy-piperidin-1-yl)-ethoxy]-6-methoxy-quinoline-3-carbonitrile	165-167	533.1 (M+H), 267.1 (M+2H) ¹²
148	4-(2-Bromo-4-chloro-phenylamino)-6-methoxy-7-(2-thiomorpholin-4-yl-ethoxy)-quinoline-3-carbonitrile	164-166	533.0 (M+H), 268.1 (M+2H) ¹²

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10	149	4-(2,4-Dichloro-5-methoxy-phenylamino)-7-[3-(2,5-dimethyl-pyrrolidin-1-yl)-propoxy]-6-methoxy-quinoline-3-carbonitrile	115-120	529.2 (M+H)
	150	4-(2,4-Dichloro-5-methoxy-phenylamino)-7-[3-(3-hydroxy-propylamino)-propoxy]-6-methoxy-quinoline-3-carbonitrile	142-147	505.2 (M+H)
15	151	1-[3-[3-Cyano-4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-quinolin-7-yloxy]-propyl]-piperidine-4-carboxylic acid ethyl ester	95-101	587.2 (M+H)
	152	7-[3-(4-acetyl-1-piperazinyl)propoxy]-4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-3-quinolincarbonitrile	115-118	558.2 (M+H)
20	153	4-(3-chloro-4-fluoroanilino)-7-methoxy-6(4-morpholiny)-3-quinolincarbonitrile		413.2 (M+H)
	154	7-[3-(4-Benzyl-piperazin-1-yl)-propoxy]-4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-quinoline-3-carbonitrile	140-142	606.2 (M+H)
25	155	4-(2,4-Dichloro-5-methoxy-phenylamino)-7-[3-(2-hydroxy-ethylamino)-propoxy]-6-methoxy-quinoline-3-carbonitrile	161-164	491.1 (M+H)
	156	4-(2,4-Dichloro-5-methoxy-phenylamino)-7-[3-[ethyl-(2-hydroxy-ethyl)-amino]-propoxy]-6-methoxy-quinoline-3-carbonitrile	162-165	519.2 (M+H)
30	157	7-[3-[Bis-(2-methoxy-ethyl)-amino]-propoxy]-4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-quinoline-3-carbonitrile	112-113	563.1 (M+H)
	158	7-[3-[Bis-(2-hydroxy-ethyl)-amino]-propoxy]-4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-quinoline-3-carbonitrile	156-159	535.1(M+H)
35	159	4-(3-chloro-4-fluoroanilino)-7-(4-morpholiny)-6-nitro-3-quinolincarbonitrile	235-239	428.1(M+H)
	160	N-[4-(3-chloro-4-fluoroanilino)-3-cyano-7-(4-morpholiny)-6-quinoliny]-2-butynamide	260-266d	464.1 (M+H)
40	161	6-amino-4-(3-chloro-4-fluoroanilino)-7-(4-morpholiny)-3-quinolincarbonitrile	amorphous	398.2 (M+H)
	162	4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-[3-{[2-(4-morpholiny)ethyl]amino}propoxy]-3-quinolincarbonitrile	75-80	560.2 (M+H)
45	163	7-[3-[(2-anilinoethyl)amino]propoxy]-4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-3-quinolincarbonitrile	90-94	566.2 (M+H)
	164	N-[4-(3-chloro-4-fluoroanilino)-3-cyano-7-(4-morpholiny)-6-quinoliny]acrylamide	amorphous	
50	165	4-(3-chloro-4-fluoroanilino)-7-[4-{[2-(dimethylamino)ethyl]-1-piperazinyl}-6-nitro-3-quinolincarbonitrile		467.2 (M+H)
	166	6-amino-4-(3-chloro-4-fluoroanilino)-7-[4-{[2-(dimethylamino)ethyl]-1-piperazinyl}-3-quinolincarbonitrile		468.2 (M+H), 234.7 (M+2H) ^a
	167	N-(4-(3-chloro-4-fluoroanilino)-3-cyano-7-{4-[2-(dimethylamino)ethyl]-1-piperazinyl}-6-quinoliny)acrylamide		522.2 (M+H), 261.7 (M+2H) ^a
	168	4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-[{2-[4-(2-methoxyethyl)-1-piperazinyl]ethyl}amino]-3-quinolincarbonitrile	53-55	559.3 (M+H), 280.2 (M+2H) ^a
	169	4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-[3-(2H-1,2,3-triazol-2-yl)propoxy]-3-quinolincarbonitrile	190-191	499.4 (M+H)
	170	4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-[3-(1H-1,2,3-triazol-1-yl)propoxy]-3-quinolincarbonitrile	188-190	499.4 (M+H)

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	171	4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-(3-thienyl)-3-quinolinecarbonitrile	215-218	456.3 (M+H)
10	172	4-[(E)-2-(2-quinolyl)ethenyl]aniline	53-54	572.5 (M+H), 286.9 (M+2H) ^a
	173	4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-[2-(2H-1,2,3-triazol-2-yl)ethyl]amino]-3-quinolinecarbonitrile	210-211	484.1 (M+H)
	174	4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-[2-(1H-1,2,3-triazol-1-yl)ethyl]amino]-3-quinolinecarbonitrile	225-228	484.1 (M+H)
15	175	4-(2,4-dichloro-5-methoxyanilino)-7-(3-thienyl)-3-quinolinecarbonitrile	211-212	426.0 (M+H)
	176	4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-[3-(1H-1,2,4-triazol-1-yl)propoxy]-3-quinolinecarbonitrile	206-208	499.1 (M+H)
	177	4-(2,4-dichloro-5-methoxyanilino)-7-[3-(1H-imidazol-1-yl)propoxy]-6-methoxy-3-quinolinecarbonitrile	155-170	498.1 (M+H), 249.6 (M+2H) ^a
20	178	4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-[3-(1H-pyrazol-1-yl)propoxy]-3-quinolinecarbonitrile	187-188	498.1 (M+H)
	179	N-[3-cyano-4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-quinoliny]-N-[4-(4-ethyl-1-piperazinyl)butyl]acetamide	57	599.2 (M+H), 300.3 (M+2H) ^a
	180	N-[3-cyano-4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-quinoliny]-N-(3-(4-ethyl-1-piperazinyl)propyl)acetamide	58.5-59	585.1 (M+H), 293.2 (M+2H) ^a
25	181	4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-[3-[4-(2-methoxyethyl)-1-piperazinyl]propoxy]-3-quinolinecarbonitrile	118-120	574.1 (M+H)
	182	4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-(1H-pyrrol-1-yl)-3-quinolinecarbonitrile	229-230	439.1 (M+H)
30	183	4-(4-bromo-2-fluoroanilino)-6-methoxy-7-[2-(1H-1,2,3-triazol-1-yl)ethoxy]-3-quinolinecarbonitrile	180-182	483.0 (M+H)
	184	4-(4-bromo-2-fluoroanilino)-6-methoxy-7-[2-(2H-1,2,3-triazol-2-yl)ethoxy]-3-quinolinecarbonitrile	93-103	483.0 (M+H)
	185	4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-[3-(1H-tetrazol-1-yl)propoxy]-3-quinolinecarbonitrile	210-214	500.1 (M+H)
35	186	4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-[3-(2H-tetrazol-2-yl)propoxy]-3-quinolinecarbonitrile	228-230	500.0 (M+H)
	187	4-(4-bromo-2-fluoroanilino)-6-methoxy-7-[2-(1H-1,2,3-triazol-1-yl)ethoxy]-3-quinolinecarbonitrile	180-184	483.0 (M+H)
	188	4-(4-bromo-2-fluoroanilino)-6-methoxy-7-[2-(2H-1,2,3-triazol-2-yl)ethoxy]-3-quinolinecarbonitrile	95-103	483.0 (M+H)
40	189	4-(2,4-dichloro-5-methoxyanilino)-7-{3-[(2-(dimethylamino)ethyl](methyl)amino]propoxy}-6-methoxy-3-quinolinecarbonitrile	85-90	532.1 (M+H), 266.7 (M+2H) ^a

Claims

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WHAT IS CLAIMED IS:

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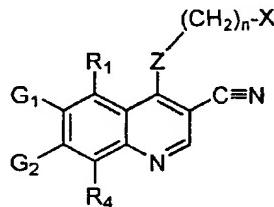
1. A compound of Formula 1 having the structure:

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wherein:



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X is cycloalkyl of 3 to 7 carbon atoms, which may be optionally substituted with one or more alkyl of 1 to 6 carbon atom groups; or is a pyridinyl, pyrimidinyl, or phenyl ring wherein the pyridinyl, pyrimidinyl, or phenyl ring may be optionally mono-, di-, or tri-substituted with a substituent selected from the group consisting of halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxylalkyl of 1-6 carbon atoms, halomethyl, alkoxyxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, carboxyalkyl of 2-7 carbon atoms, carboalkoxyalkyl of 3-8 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-10 carbon atoms, N-alkylaminoalkoxy of 2-9 carbon atoms, N,N-dialkylaminoalkoxy of 3-10 carbon atoms, mercapto, and benzoylamino;

Z is -NH-, -O-, -S-, or -NR- ;

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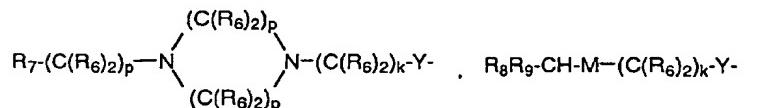
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R is alkyl of 1-6 carbon atoms, or carboalkyl of 2-7 carbon atoms;

10 G₁, G₂, R₁, and R₄ are each, independently, hydrogen, halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkenyloxy of 2-6 carbon atoms, alkynyoxy of 2-6 carbon atoms, hydroxymethyl, halomethyl, alkanoyloxy of 1-6 carbon atoms, alkenoyloxy of 3-8 carbon atoms, alkynoyloxy of 3-8 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkenoyloxymethyl of 4-9 carbon atoms, alkynoyloxymethyl of 4-9 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, alkylsulphinyl of 1-6 carbon atoms, alkylsulphonyl of 1-6 carbon atoms, alkylsulfonamido of 1-6 carbon atoms, alkenylsulfonamido of 2-6 carbon atoms, alkynylsulfonamido of 2-6 carbon atoms, hydroxy, trifluoromethyl, trifluoromethoxy, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzyl, amino, hydroxyamino, alkoxyamino of 1-4 carbon atoms, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, N-alkylcarbamoyl, N,N-dialkylcarbamoyl, N-alkyl-N-alkenylamino of 4 to 12 carbon atoms, N,N-dialkenylamino of 6-12 carbon atoms, phenylamino, benzylamino,

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20 R₇-(C(R₆)₂)_g-Y-, R₇-(C(R₆)₂)_p-M-(C(R₆)₂)_k-Y-, or Het-(C(R₆)₂)_q-W-(C(R₆)₂)_k-Y-

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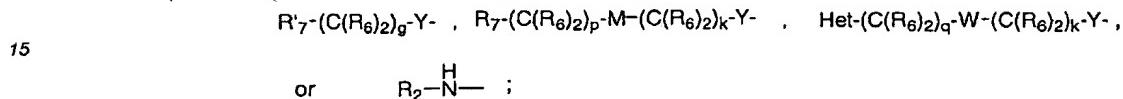
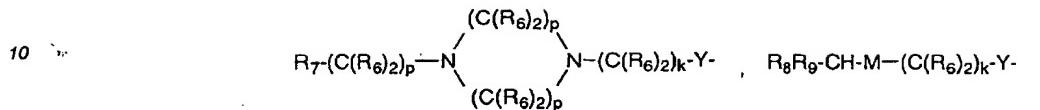
with the proviso that either G₁ or G₂ or both G₁ and G₂ must be a radical selected from the group

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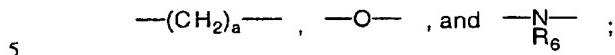
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20 Y is a divalent radical selected from the group consisting of



30 R_7 is $-\text{NR}_6\text{R}_6$, $-\text{J}$, $-\text{OR}_6$, $-\text{N}(\text{R}_6)_3^+$, or $-\text{NR}_6(\text{OR}_6)$;

35 R'_7 is $-\text{NR}_6(\text{OR}_6)$, $-\text{N}(\text{R}_6)_3^+$, alkenoxy of 1-6 carbon atoms, alkynoxy of 1-6 carbon atoms, N-alkyl-N-alkenylamino of 4 to 12 carbon atoms, N,N-dialkenylamino of 6-12

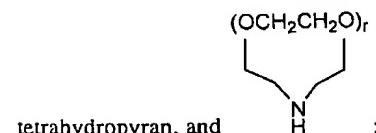
40 10 carbon atoms, N-alkyl-N-alkynylamino of 4 to 12 carbon atoms, N-alkenyl-N-alkynylamino of 4 to 12 carbon atoms, or N,N-dialkynylamino of 6-12 carbon atoms with the proviso that the alkenyl or alkynyl moiety is bound to a nitrogen or oxygen atom through a saturated carbon atom;

45 M is $>\text{NR}_6$, $-\text{O-}$, $>\text{N-(C}(\text{R}_6)_2)_p\text{NR}_6\text{R}_6$, or $>\text{N-(C}(\text{R}_6)_2)_p\text{-OR}_6$;

50 15 W is $>\text{NR}_6$, $-\text{O-}$ or is a bond;

55 Het is a heterocycle selected from the group consisting of morpholine, thiomorpholine, thiomorpholine S-oxide, thiomorpholine S,S-dioxide, piperidine, pyrrolidine, aziridine, pyridine, imidazole, 1,2,3-triazole, 1,2,4-triazole, thiazole, thiazolidine, tetrazole, piperazine, furan, thiophene,

60 20 tetrahydrothiophene, tetrahydrofuran, dioxane, 1,3-dioxolane ,



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10 wherein the heterocycle is optionally mono- or di-substituted on carbon or
nitrogen with R₆, optionally mono- or di-substituted on carbon with hydroxy,
-N(R₆)₂, or -OR₆, optionally mono or di-substituted on carbon with the
mono-valent radicals -(C(R₆)₂)_sOR₆ or -(C(R₆)₂)_sN(R₆)₂, or optionally
15 5 mono or di-substituted on a saturated carbon with divalent radicals -O- or
-O(C(R₆)₂)_sO-;

20 R₆ is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-
6 carbon atoms, cycloalkyl of 1-6 carbon atoms, carboalkyl of 2-7 carbon
10 atoms, carboxyalkyl (2-7 carbon atoms), phenyl, or phenyl optionally
substituted with one or more halogen, alkoxy of 1-6 carbon atoms,
25 trifluoromethyl, amino, alkylamino of 1-3 carbon atoms, dialkylamino of 2-6
carbon atoms, nitro, cyano, azido, halomethyl, alkoxymethyl of 2-7 carbon
atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkylthio of 1-6 carbon
30 15 atoms, hydroxy, carboxyl, carboalkoxy of 2-7 carbon atoms, phenoxy, phenyl,
thiophenoxy, benzoyl, benzyl, phenylamino, benzylamino, alkanoylamino of
1-6 carbon atoms, or alkyl of 1-6 carbon atoms;

35 R₂, is selected from the group consisting of

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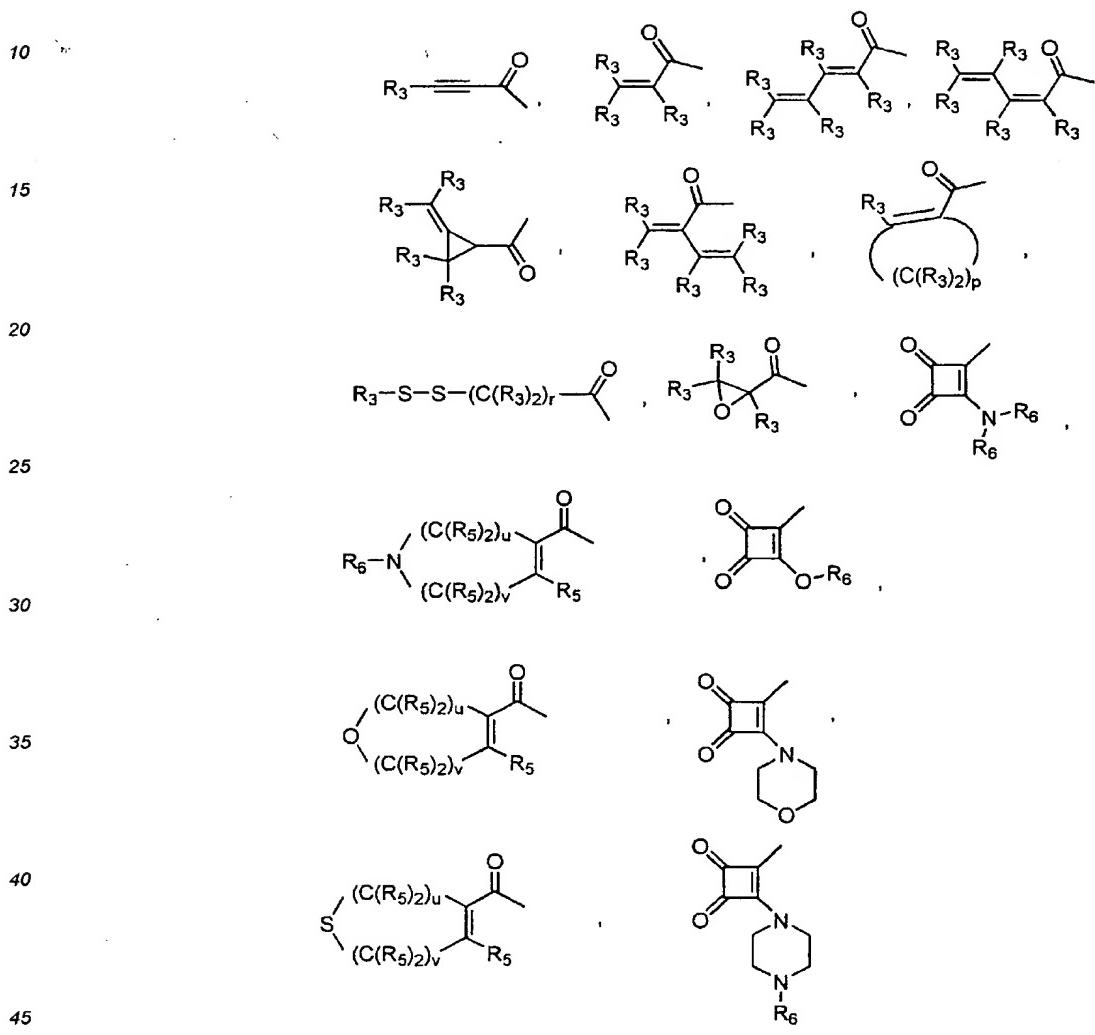
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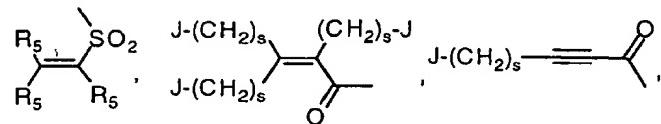
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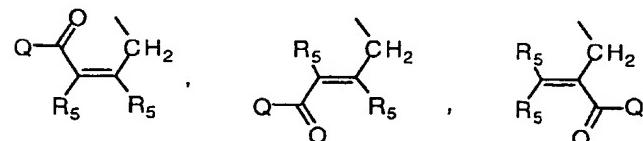
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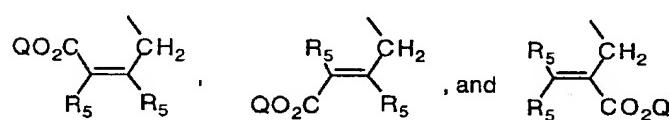
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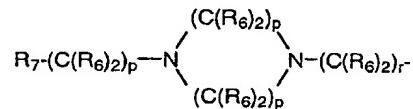
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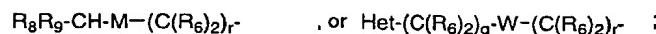
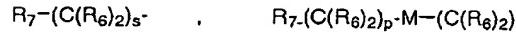
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R3 is independently hydrogen, alkyl of 1-6 carbon atoms, carboxy, carboalkoxy of 1-6 carbon atoms, phenyl, carboalkyl of 2-7 carbon atoms,

3



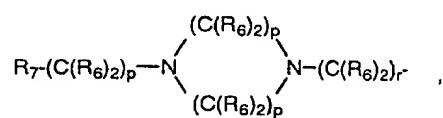
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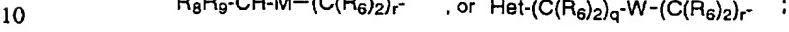
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with the proviso that at least one of the R₃ groups is selected from the group

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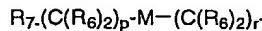
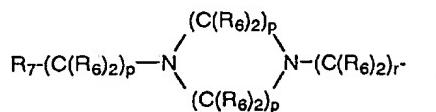


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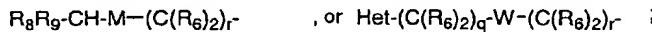
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R₅ is independently hydrogen, alkyl of 1-6 carbon atoms, carboxy, carboalkoxy of
 10 1-6 carbon atoms, phenyl, carboalkyl of 2-7 carbon atoms,

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$$\text{, or Het-(C(R_6)_2)_q-W-(C(R_6)_2)_r- ;}$$

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R₈, and R₉ are each, independently, -(C(R₆)₂)_tNR₆R₆, or -(C(R₆)₂)_rOR₆;

J is independently hydrogen, chlorine, fluorine, or bromine;

25

Q is alkyl of 1-6 carbon atoms or hydrogen;

a = 0 or 1;

10 g = 1-6;

k = 0-4;

n is 0-1;

p = 2-4;

q=0-4;

35 15 r = 1-4;

s = 1-6;

u = 0-4 and v = 0-4 , wherein the sum of u+v is 2-4;

40

or a pharmaceutically acceptable salt thereof,

provided that

20 when R₆ is alkenyl of 2-7 carbon atoms or alkynyl of 2-7 carbon atoms, such
 alkenyl or alkynyl moiety is bound to a nitrogen or oxygen atom
 45 through a saturated carbon atom;

and further provided that

when Y is -NR₆- and R₇ is -NR₆R₆, -N(R₆)₃ , or -NR₆(OR₆), then g = 2-6;

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25 when M is -O- and R₇ is -OR₆, then p = 1-4;

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when Y is -NR₆-, then k = 2-4;
when Y is -O- and M or W is -O-, then k = 1-4;
when W is not a bond with Het bonded through a nitrogen atom, then q = 2-4;
and when W is a bond with Het bonded through a nitrogen atom and Y is -O-
or -NR₆-, then k = 2-4.

2. The compound according to claim 1 wherein Z is -NH- and n = 0 or a pharmaceutically acceptable salt thereof.

10 3. The compound according to claim 2 wherein X is optionally substituted phenyl or a pharmaceutically acceptable salt thereof.

20 4. The compound according to claim 3 wherein R₁ and R₄ are hydrogen or a pharmaceutically acceptable salt thereof.

25 5. The compound according to claim 1, which is:

30 a) 1-Methyl-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid [4-(3-bromo-phenylamino)-3-cyano-quinolin-6-yl]-amide or a pharmaceutically acceptable salt thereof;

35 b) N-[4-[(3-Bromophenyl)amino]-3-cyano-6-quinoliny]-4-(N-allyl-N-methylamino)-2-butynamide or a pharmaceutically acceptable salt thereof;

40 c) N-[4-[(3-Bromophenyl)amino]-3-cyano-6-quinoliny]-4-(N-methoxyethyl-N-methylamino)-2-butynamide or a pharmaceutically acceptable salt thereof;

45 d) N-[4-[(3-Bromophenyl)amino]-3-cyano-6-quinoliny]-4-(bis-(2-methoxyethyl)amino)-2-butynamide or a pharmaceutically acceptable salt thereof;

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10 e) 4-Methoxymethoxy-but-2-yoic acid [4-(3-bromo-phenylamino)-3-cyano-
quinolin-6-yl]-amide or a pharmaceutically acceptable salt thereof;

15 f) 4-(4-Chloro-2-fluoro-phenylamino)-6-methoxy-7-(2-pyridin-4-yl-ethoxy)-
quinoline-3-carbonitrile or a pharmaceutically acceptable salt thereof;

20 g) 4-(2-Methoxy-ethoxy)-but-2-yoic acid [4-(3-bromo-phenylamino)-3- cyano-
quinolin-6-yl]-amide or a pharmaceutically acceptable salt thereof;

25 10 h) 4-((2S)-2-Methoxymethylpyrrolidin-1-yl)but-2-yoic Acid [4-(3-
bromophenylamino)-3-cyanoquinolin-6-yl]amide or a pharmaceutically
acceptable salt thereof;

30 15 i) 4-(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)but-2-yoic Acid [4-(3-
Bromophenylamino)-3-cyanoquinolin-6-yl] amide or a pharmaceutically
acceptable salt thereof;

35 20 j) 4-(3-Bromo-phenylamino)-6-(2-ethoxy-3,4-dioxo-cyclobut-1-enylamino)-
quinoline-3-carbonitrile or a pharmaceutically acceptable salt thereof;

40 25 k) 4-[(2-Methoxy-ethyl)-methyl-amino]-but-2-enoic acid [4-(3-chloro-4- fluor-
phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide or a pharmaceutically
acceptable salt thereof;

45 25 l) (S)-4-(2-Methoxymethyl-pyrrolidin-1-yl)-but-2-enoic acid [4-(3-chloro-4-
fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide
dihydrochloride or a pharmaceutically acceptable salt thereof;

50 30 m) 4-(3-Hydroxymethyl-piperidin-1-yl)-but-2-enoic acid [4-(3-chloro-4- fluoro-
phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide or a pharmaceutically
acceptable salt thereof;

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- 10 n) 4-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide or a pharmaceutically acceptable salt thereof;
- 15 o) 4-(2-Hydroxymethyl-piperidin-1-yl)-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide or a pharmaceutically acceptable salt thereof;
- 20 p) 4-Bromo-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide or a pharmaceutically acceptable salt thereof;
- 25 q) 4-(3-hydroxy-4-methyl-phenylamino)-6-methoxy-7-(3-pyridin-4-yl-propoxy)-quinoline-3-carbonitrile or a pharmaceutically acceptable salt thereof;
- 30 r) 4-Diallylamino-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3cyano-7-methoxy-quinolin-6-yl]-amide or a pharmaceutically acceptable salt thereof;
- 35 s) 4-[Bis-(2-methoxy-ethyl)-amino]-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide or a pharmaceutically acceptable salt thereof;
- 40 t) 4-([1,3]Dioxolan-2-ylmethyl-methyl-amino)-but-2-enoic acid
- 45 3-cyano-7-methoxy-quinolin-6-yl]-amide or a pharmaceutically acceptable salt thereof;
- 50 u) 4-[Bis-(2-hydroxy-ethyl)-amino]-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide or a pharmaceutically acceptable salt thereof;

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- 10 v) 4-Thiomorpholin-4-yl-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide or a pharmaceutically acceptable salt thereof;
- 15 5 w) 4-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide or a pharmaceutically acceptable salt thereof;
- 20 10 x) 4-(1,4,7-Trioxa-10-aza-cyclododec-10-yl)-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide or a pharmaceutically acceptable salt thereof;
- 25 15 y) 4-(Methoxy-methyl-amino)-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide or a pharmaceutically acceptable salt thereof;
- 30 20 z) 4-(4-Hydroxy-piperidin-1-yl)-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide or a pharmaceutically acceptable salt thereof;
- 35 25 aa) 4-[1,4']Bipiperidinyl-1'-yl-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide or a pharmaceutically acceptable salt thereof;
- 40 45 bb) 4-Thiazolidin-3-yl-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide or a pharmaceutically acceptable salt thereof;
- 50 55 cc) 3-(3-[4-(3-Chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-ylcarbamoyl]-allyl)-4-methyl-thiazol-3-ium bromide or a pharmaceutically acceptable salt thereof;

- 10 dd) 4-(2,6-Dimethyl-piperidin-1-yl)-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide or a pharmaceutically acceptable salt thereof;
- 15 ee) 4-[Bis-(2-hydroxy-propyl)-amino]-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide or a pharmaceutically acceptable salt thereof;
- 20 ff) 4-(3-Hydroxy-pyrrolidin-1-yl)-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide or a pharmaceutically acceptable salt thereof;
- 25 gg) 4-[(2-Hydroxy-ethyl)-methyl-amino]-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide or a pharmaceutically acceptable salt thereof;
- 30 hh) 4-(2,5-Dimethyl-pyrrolidin-1-yl)-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide or a pharmaceutically acceptable salt thereof;
- 35 ii) 4-(4,4-Dihydroxy-piperidin-1-yl)-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide or a pharmaceutically acceptable salt thereof;
- 40 jj) 4-(3-Chloro-4-fluoro-phenylamino)-7-methoxy-6-pyrrolidin-1-yl-quinoline-3-carbonitrile or a pharmaceutically acceptable salt thereof;
- 45 kk) 4-(3-Chloro-4-fluroanilino)-7-methoxy-6-(1H-pyrrol-1-yl)-3-quinolinecarbonitrile or a pharmaceutically acceptable salt thereof;
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- 10 ll) 6-(1-Aziridinyl)-4-(3-chloro-4-fluoroanilino)-7-methoxy-3-
quinolinecarbonitrile or a pharmaceutically acceptable salt thereof;
- 15 mm) 4-[(2-Methoxy-ethyl)-methyl-amino]-but-2-enoic acid [4-(3-bromo-
phenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]-amide or a pharmaceutically
acceptable salt thereof;
- 20 nn) 4-(2,4-Dichloro-5-methoxy-phenylamino)-7-[3-(4-hydroxy-piperidin-1-yl)-
propoxy]-6-methoxy-quinoline-3-carbonitrile or a pharmaceutically
acceptable salt thereof;
- 25 oo) 4-(2,4-Dichloro-5-methoxy-phenylamino)-7-{3-[4-(2-hydroxy-ethyl)-
piperazin-1-yl]-propoxy}-6-methoxy-quinoline-3-carbonitrile or a
pharmaceutically acceptable salt thereof;
- 30 pp) 4-(2-Bromo-4-chloro-phenylamino)-7-{2-[(2-hydroxy-ethyl)-methyl-amino]-
ethoxy}-6-methoxy-quinoline-3-carbonitrile or a pharmaceutically acceptable
salt thereof;
- 35 20 qq) 4-(2,4-Dichloro-5-methoxy-phenylamino)-7-{3-[(2-hydroxy-ethyl)-methyl-
amino]-propoxy}-6-methoxy-quinoline-3-carbonitrile or a pharmaceutically
acceptable salt thereof;
- 40 rr) 4-(2,4-Dichloro-5-methoxy-phenylamino)-6-methoxy-7-(3-thiomorpholin-4-
yl-propoxy)-quinoline-3-carbonitrile or a pharmaceutically acceptable salt
thereof;
- 45 ss) 4-(2,4-Dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(2-methoxy-
ethylamino)-propoxy]-quinoline-3-carbonitrile or a pharmaceutically
acceptable salt thereof;

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- 10 tt) 4-(2,4-Dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperidin-1-yl)-propoxy]-quinoline-3-carbonitrile or a pharmaceutically acceptable salt thereof;
- 15 5 uu) 4-(2,4-Dichloro-5-methoxy-phenylamino)-7-[3-(2,6-dimethyl-morpholin-4-yl)-propoxy]-6-methoxy-quinoline-3-carbonitrile or a pharmaceutically acceptable salt thereof;
- 20 10 vv) 4-(2-Bromo-4-chloro-phenylamino)-7-{2-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-ethoxy}-6-methoxy-quinoline-3-carbonitrile or a pharmaceutically acceptable salt thereof;
- 25 15 ww) 4-(2-Bromo-4-chloro-phenylamino)-7-[2-(4-hydroxy-piperidin-1-yl)-ethoxy]-6-methoxy-quinoline-3-carbonitrile or a pharmaceutically acceptable salt thereof;
- 30 30 xx) 4-(2-Bromo-4-chloro-phenylamino)-6-methoxy-7-(2-thiomorpholin-4-yl-ethoxy)-quinoline-3-carbonitrile or a pharmaceutically acceptable salt thereof;
- 35 20 yy) 4-(2,4-Dichloro-5-methoxy-phenylamino)-7-[3-(2,5-dimethyl-pyrrolidin-1-yl)-propoxy]-6-methoxy-quinoline-3-carbonitrile or a pharmaceutically acceptable salt thereof;
- 40 25 zz) 4-(2,4-Dichloro-5-methoxy-phenylamino)-7-[3-(3-hydroxy-propylamino)-propoxy]-6-methoxy-quinoline-3-carbonitrile or a pharmaceutically acceptable salt thereof;
- 45 30 aaa) 1-{3-[3-Cyano-4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-quinolin-7-yloxy]-propyl}-piperidine-4-carboxylic acid ethyl ester or a pharmaceutically acceptable salt thereof;

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- 10 bbb) 7-[3-(4-acetyl-1-piperazinyl)propoxy]-4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-3-quinolinecarbonitrile or a pharmaceutically acceptable salt thereof;
- 15 ccc) 4-(3-chloro-4-fluoroanilino)-7-methoxy-6(4-morpholinyl)-3-quinolinecarbonitrile or a pharmaceutically acceptable salt thereof;
- 20 ddd) 7-[3-(4-Benzyl-piperazin-1-yl)-propoxy]-4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-quinoline-3-carbonitrile or a pharmaceutically acceptable salt thereof;
- 25 eee) 4-(2,4-Dichloro-5-methoxy-phenylamino)-7-[3-(2-hydroxy-ethylamino)-prooxy]-6-methoxy-quinoline-3-carbonitrile or a pharmaceutically acceptable salt thereof;
- 30 fff) 4-(2,4-Dichloro-5-methoxy-phenylamino)-7-[3-[ethyl-(2-hydroxy-ethyl)-amino]-propoxy]-6-methoxy-quinoline-3-carbonitrile or a pharmaceutically acceptable salt thereof;
- 35 ggg) 7-[3-[Bis-(2-methoxy-ethyl)-amino]-propoxy]-4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-quinoline-3-carbonitrile or a pharmaceutically acceptable salt thereof;
- 40 hhh) 7-[3-[Bis-(2-hydroxy-ethyl)-amino]-propoxy]-4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-quinoline-3-carbonitrile or a pharmaceutically acceptable salt thereof;
- 45 iii) 4-(3-chloro-4-fluoroanilino)-7-(4-morpholinyl)-6-nitro-3-quinolinecarbonitrile or a pharmaceutically acceptable salt thereof;
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- 10 jjj) N-[4-(3-chloro-4-fluoroanilino)-3-cyano-7-(4-morpholinyl)-6-quinolinyl]-2-butynamide or a pharmaceutically acceptable salt thereof;
- 15 kkk) 6-amino-4-(3-chloro-4-fluoroanilino)-7-(4-morpholinyl)-3-quinoliniccarbonitrile or a pharmaceutically acceptable salt thereof;
- 20 III) 4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-(3-{[2-(4--morpholinyl)ethyl]amino}propoxy)-3-quinolinecarbonitrile or a pharmaceutically acceptable salt thereof;
- 25 mmm) 7-{3-[(2-anilinoethyl)amino]propoxy}-4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-3-quinoliniccarbonitrile or a pharmaceutically acceptable salt thereof;
- 30 nnn) N-[4-(3-chloro-4-fluoroanilino)-3-cyano-7-(4-morpholinyl)-6-quinolinyl]acrylamide or a pharmaceutically acceptable salt thereof;
- 35 ooo) 4-(3-chloro-4-fluoroanilino)-7-{4-[2-(dimethylamino)ethyl]-1-piperazinyl}-6-nitro-3-quinolinecarbonitrile or a pharmaceutically acceptable salt thereof;
- 40 ppp) 6-amino-4-(3-chloro-4-fluoroanilino)-7-{4-[2-(dimethylamino)ethyl]-1-piperazinyl}-3-quinolinecarbonitrile or a pharmaceutically acceptable salt thereof;
- 45 qqq) N-(4-(3-chloro-4-fluoroanilino)-3-cyano-7-{4-[2-(dimethylamino)ethyl]-1-piperazinyl}-6-quinolinyl)acrylamide or a pharmaceutically acceptable salt thereof;
- 50 rrr) 4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-{(2-[4-(2-methoxyethyl)-1-piperazinyl]ethyl)amino}-3-quinolinecarbonitrile or a pharmaceutically acceptable salt thereof;

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- 10 sss) 4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-[3-(2H-1,2,3-triazol-2-yl)propoxy]-3-quinolinecarbonitrile or a pharmaceutically acceptable salt thereof;
- 15 5 ttt) 4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-[3-(1H-1,2,3-triazol-1-yl)propoxy]-3-quinolinecarbonitrile or a pharmaceutically acceptable salt thereof;
- 20 20 uuu) 4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-(3-thienyl)-3-quinolinecarbonitrile or a pharmaceutically acceptable salt thereof;
- 25 25 vvv) 4-[(E)-2-(2-quinolinyloxy)ethenyl]aniline or a pharmaceutically acceptable salt thereof;
- 30 15 www) 4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-{[2-(2H-1,2,3-triazol-2-yl)ethyl]amino}-3-quinolinecarbonitrile or a pharmaceutically acceptable salt thereof;
- 35 35 xxx) 4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-{[2-(1H-1,2,3-triazol-1-yl)ethyl]amino}-3-quinolinecarbonitrile or a pharmaceutically acceptable salt thereof;
- 40 40 yyy) 4-(2,4-dichloro-5-methoxyanilino)-7-(3-thienyl)-3-quinolinecarbonitrile or a pharmaceutically acceptable salt thereof;
- 45 25 zzz) 4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-[3-(1H-1,2,4-triazol-1-yl)propoxy]-3-quinolinecarbonitrile or a pharmaceutically acceptable salt thereof;
- 50 50 30 aaaa) 4-(2,4-dichloro-5-methoxyanilino)-7-[3-(1H-imidazol-1-yl)propoxy]-6-methoxy-3-quinolinecarbonitrile or a pharmaceutically acceptable salt thereof;

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- 10 bbbb) 4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-[3-(1H-pyrazol-1-yl)propoxy]-3-quinolinecarbonitrile or a pharmaceutically acceptable salt thereof;
- 15 cccc) N-[3-cyano-4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-quinolinyl]-N-[4-(4-ethyl-1-piperazinyl)butyl]acetamide or a pharmaceutically acceptable salt thereof;
- 20 10 dddd) N-[3-cyano-4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-quinolinyl]-N-(3-(4-ethyl-1-piperazinyl)propyl)acetamide or a pharmaceutically acceptable salt thereof;
- 25 15 eeee) 4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-[3-[4-(2-methoxyethyl)-1-piperazinyl]propoxy]-3-quinolinecarbonitrile or a pharmaceutically acceptable salt thereof;
- 30 35 ffff) 4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-(1H-pyrrol-1-yl)-3-quinolinecarbonitrile or a pharmaceutically acceptable salt thereof;
- 40 20 gggg) 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-[2-(1H-1,2,3-triazol-1-yl)ethoxy]-3-quinolinecarbonitrile or a pharmaceutically acceptable salt thereof;
- 45 25 hhhh) 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-[2-(2H-1,2,3-triazol-2-yl)ethoxy]-3-quinolinecarbonitrile or a pharmaceutically acceptable salt thereof;
- 50 30 iiiii) 4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-[3-(1H-tetraazol-1-yl)propoxy]-3-quinolinecarbonitrile or a pharmaceutically acceptable salt thereof;

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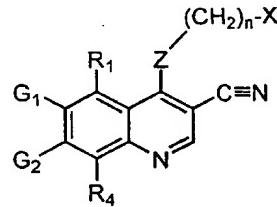
10 jjii) 4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-[3-(2H-tetraazol-2-yl)propoxy]-3-quinolinecarbonitrile or a pharmaceutically acceptable salt thereof;

15 5 kkkk) 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-[2-(1H-1,2,3-triazol-1-yl)ethoxy]-3-quinolinecarbonitrile or a pharmaceutically acceptable salt thereof;

20 20 IIII) 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-[2-(2H-1,2,3-triazol-2-yl)ethoxy]-3-quinolinecarbonitrile or a pharmaceutically acceptable salt thereof; or

25 10 mmmm) 4-(2,4-dichloro-5-methoxyanilino)-7-{3-[[2-(dimethylamino)ethyl](methyl)amino]propoxy}-6-methoxy-3-quinolinecarbonitrile or a pharmaceutically acceptable salt thereof.

30 15 6. A method of treating, inhibiting the growth of, or eradicating a neoplasm in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of formula 1 having the structure



40 20 wherein:

45 45 X is cycloalkyl of 3 to 7 carbon atoms, which may be optionally substituted with one or more alkyl of 1 to 6 carbon atom groups; or is a pyridinyl, pyrimidinyl, or phenyl ring wherein the pyridinyl, pyrimidinyl, or phenyl ring may be optionally mono-, di-, or tri-substituted with a substituent selected from the

50 50 25 group consisting of halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon

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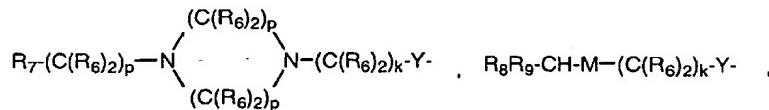
- 10 atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, carboxyalkyl of 2-7 carbon atoms, carboalkoxyalkyl of 3-8 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-10 carbon atoms, N-alkylaminoalkoxy of 2-9 carbon atoms, N,N-dialkylaminoalkoxy of 3-10 carbon atoms, mercapto, and benzoylamino;
- Z is -NH-, -O-, -S-, or -NR-;
- 15 15 R is alkyl of 1-6 carbon atoms, or carboalkyl of 2-7 carbon atoms;
- 30 G₁, G₂, R₁, and R₄ are each, independently, hydrogen, halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkenyloxy of 2-6 carbon atoms, alkynyoxy of 2-6 carbon atoms, hydroxymethyl, halomethyl, alkanoyloxy of 1-6 carbon atoms, alkenoyloxy of 3-8 carbon atoms, alkynoyloxy of 3-8 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkenoyloxymethyl of 4-9 carbon atoms, alkynoyloxymethyl of 4-9 carbon atoms, alkoxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, alkylsulphinyl of 1-6 carbon atoms, alkylsulphonyl of 1-6 carbon atoms, alkylsulfonamido of 1-6 carbon atoms, alkenylsulfonamido of 2-6 carbon atoms, alkynylsulfonamido of 2-6 carbon atoms, hydroxy, trifluoromethyl, trifluoromethoxy, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzyl, amino, hydroxyamino, alkoxyamino of 1-4 carbon atoms, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, N-alkylcarbamoyl, N,N-dialkylcarbamoyl, N-alkyl-N-
- 35 20
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- 45
- 50 30

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10 alkenylamino of 4 to 12 carbon atoms, N,N-dialkenylamino of 6-12 carbon atoms, phenylamino, benzylamino,

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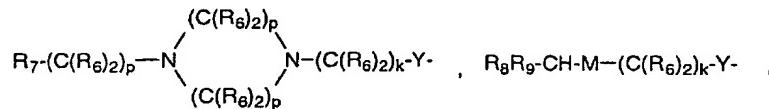


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R₇-(C(R₆)₂)_g-Y-, R₇-(C(R₆)₂)_p-M-(C(R₆)₂)_k-Y-, or Het-(C(R₆)₂)_q-W-(C(R₆)₂)_k-Y-

5 with the proviso that either G₁ or G₂ or both G₁ and G₂ must be a radical selected from the group

25



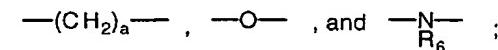
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R'₇-(C(R₆)₂)_g-Y-, R₇-(C(R₆)₂)_p-M-(C(R₆)₂)_k-Y-, Het-(C(R₆)₂)_q-W-(C(R₆)₂)_k-Y-,

or R₂-N—;

35

10 Y is a divalent radical selected from the group consisting of



40

R₇ is -NR₆R₆, -J, -OR₆, -N(R₆)₃⁺, or -NR₆(OR₆);

15 R'₇ is -NR₆(OR₆), -N(R₆)₃⁺, alkenoxy of 1-6 carbon atoms, alkynoxy of 1-6 carbon atoms, N-alkyl-N-alkenylamino of 4 to 12 carbon atoms, N,N-dialkenylamino

45

atoms, N-alkyl-N-alkynylamino of 4 to 12 carbon atoms, N-alkenyl-N-alkynylamino of 4 to 12 carbon atoms, or N,N-dialkynylamino of 6-12 carbon atoms with the proviso that the alkenyl or alkynyl moiety is bound to a nitrogen or oxygen atom through a saturated carbon atom;

20 M is >NR₆, -O-, >N-(C(R₆)₂)_pNR₆R₆, or >N-(C(R₆)₂)_p-OR₆;

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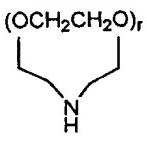
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W is $>\text{NR}_6$, $-\text{O}-$ or a bond;

10 Het is a heterocycle selected from the group consisting of morpholine, thiomorpholine, thiomorpholine S-oxide, thiomorpholine S,S-dioxide, piperidine, pyrrolidine, aziridine, pyridine, imidazole, 1,2,3-triazole, 1,2,4-
15 triazole, thiazole, thiazolidine, tetrazole, piperazine, furan, thiophene, tetrahydrothiophene, tetrahydrofuran, dioxane, 1,3-dioxolane

20 
tetrahydropyran, and ;
wherein the heterocycle is optionally mono- or di-substituted on carbon or
nitrogen with R₆, optionally mono- or di-substituted on carbon with hydroxy,
25 -N(R₆)₂, or -OR₆, optionally mono or di-substituted on carbon with the
mono-valent radicals -(C(R₆)₂)₅OR₆ or -(C(R₆)₂)₅N(R₆)₂, or optionally
mono or di-substituted on a saturated carbon with divalent radicals -O- or -
30 O(C(R₆)₂)₅O-;

R₆ is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-
15 6 carbon atoms, cycloalkyl of 1-6 carbon atoms, carboalkyl of 2-7 carbon
atoms, carboxyalkyl (2-7 carbon atoms), phenyl, or phenyl optionally
35 substituted with one or more halogen, alkoxy of 1-6 carbon atoms,
trifluoromethyl, amino, alkylamino of 1-3 carbon atoms, dialkylamino of 2-6
carbon atoms, nitro, cyano, azido, halomethyl, alkoxyethyl of 2-7 carbon
atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkylthio of 1-6 carbon
40 atoms, hydroxy, carboxyl, carboalkoxy of 2-7 carbon atoms, phenoxy, phenyl,
thiophenoxy, benzoyl, benzyl, phenylamino, benzylamino, alkanoylamino of
45 1-6 carbon atoms, or alkyl of 1-6 carbon atoms;

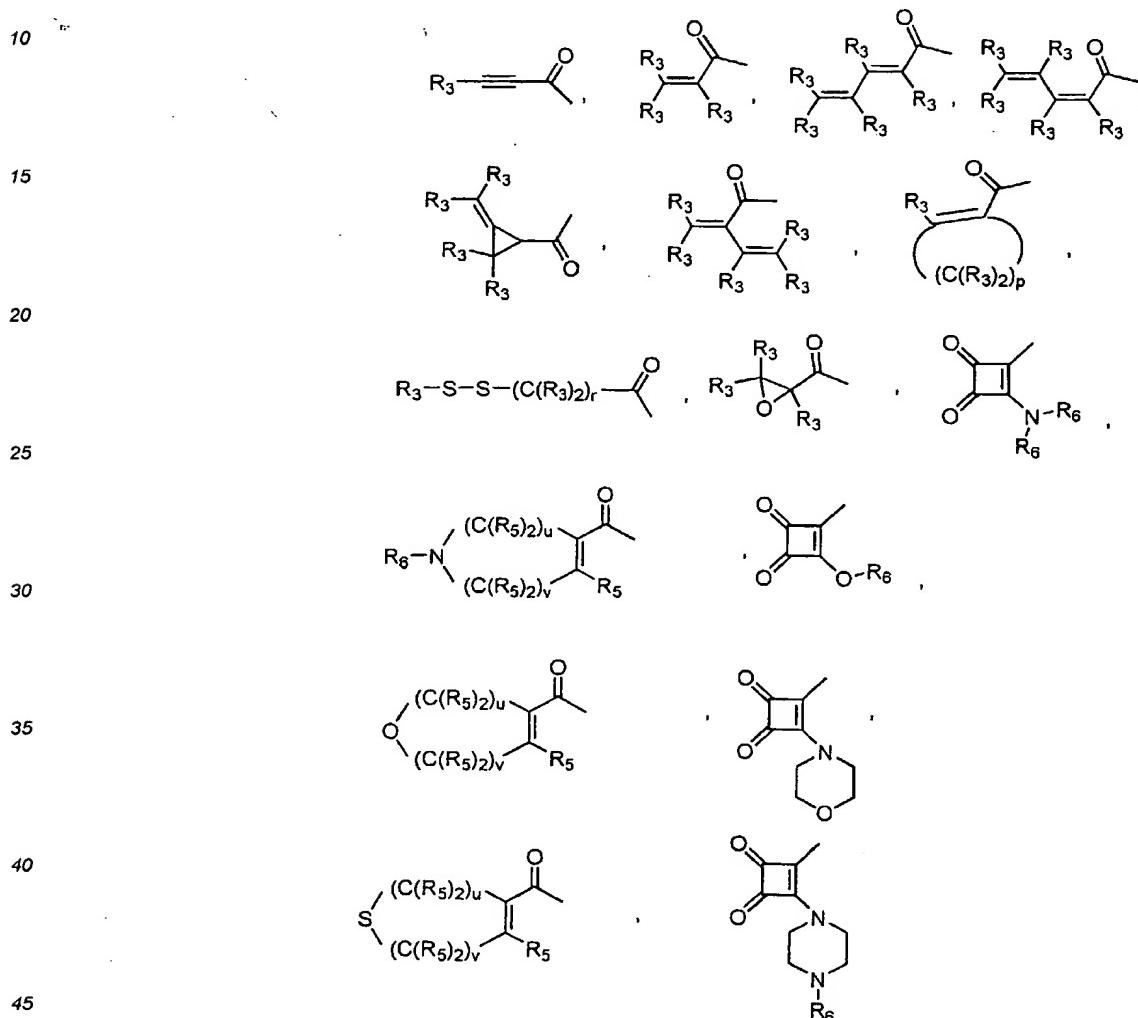
R₂, is selected from the group consisting of

25

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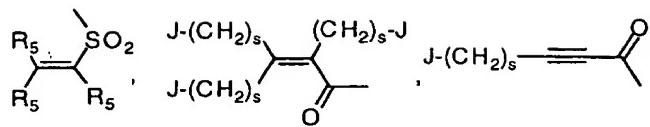
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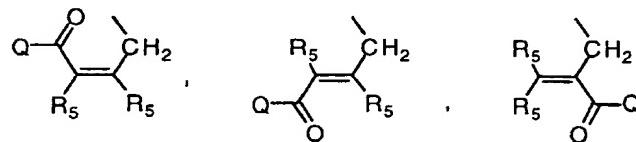
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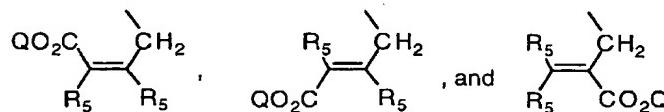
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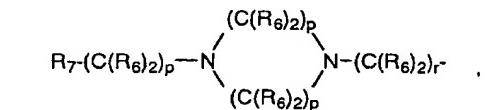
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R₃ is independently hydrogen, alkyl of 1-6 carbon atoms, carboxy, carboalkoxy or

1-6 carbon atoms, phenyl, carboalkyl of 2-7 carbon atoms.

30

35



$$R_7-(C(R_6)_2)_s- \quad , \quad R_7-(C(R_6)_2)_p-M-(C(R_6)_2)_q$$

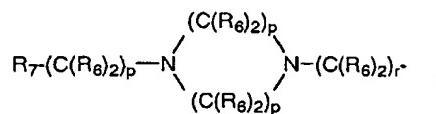
R₈R₉-CH-M-(C(R₆)₂)_r- , or Het-(C(R₆)₂)_g-W-(C(R₆)₂)_r-

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with the proviso that at least one of the R₃ groups is selected from the group

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45



$$R'_7-(C(R_6)_2)_9- \quad , \quad R_7.(C(R_6)_2)_p-M-(C(R_6)_2)_q-$$

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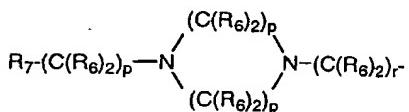
R₈R₉-CH-M-(C(R₆)₂)_r, or Het-(C(R₆)₂)_s-W-(C(R₆)₂)_t

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R₅ is independently hydrogen, alkyl of 1-6 carbon atoms, carboxy, carboalkoxy of 1-6 carbon atoms, phenyl, carboalkyl of 2-7 carbon atoms,

15



20



25

R₈, and R₉ are each, independently, -(C(R₆)₂)_rNR₆R₆, or -(C(R₆)₂)_rOR₆;

J is independently hydrogen, chlorine, fluorine, or bromine;

Q is alkyl of 1-6 carbon atoms or hydrogen;

10 a = 0 or 1;

30

g = 1-6;

k = 0-4;

n is 0-1;

p = 2-4;

35

q=0-4;

r = 1-4;

s = 1-6;

40

u = 0-4 and v = 0-4 , wherein the sum of u+v is 2-4;

or a pharmaceutically acceptable salt thereof,

20 provided that

45

when R₆ is alkenyl of 2-7 carbon atoms or alkynyl of 2-7 carbon atoms, such alkenyl or alkynyl moiety is bound to a nitrogen or oxygen atom through a saturated carbon atom;

and further provided that

50

25 when Y is -NR₆- and R₇ is -NR₆R₆, -N(R₆)₃ , or -NR₆(OR₆), then g = 2-6;

when M is -O- and R₇ is -OR₆, then p = 1-4;

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when Y is -NR₆-, then k = 2-4;

when Y is -O- and M or W is -O-, then k = 1-4;

when W is not a bond with Het bonded through a nitrogen atom, then q = 2-4;

and when W is a bond with Het bonded through a nitrogen atom and Y is -O- or

5 -NR₆-, then k = 2-4.

10

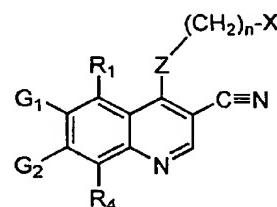
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7. The method according to claim 6 wherein the neoplasm is selected from the group consisting of breast, kidney, bladder, mouth, larynx, esophagus, stomach, colon, ovary, and lung.

8. A method of treating, inhibiting the progression of, or eradicating polycystic kidney disease in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of formula 1 having the structure



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35

15

wherein:

X is cycloalkyl of 3 to 7 carbon atoms, which may be optionally substituted with one or more alkyl of 1 to 6 carbon atom groups; or is a pyridinyl, pyrimidinyl, or phenyl ring wherein the pyridinyl, pyrimidinyl, or phenyl ring may be optionally mono-, di-, or tri-substituted with a substituent selected from the group consisting of halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxylalkyl of 1-6 carbon atoms, halomethyl, alkoxyxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon

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10 atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, carboxyalkyl of 2-7 carbon atoms, carboalkoxyalkyl of 3-8 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-10 carbon atoms, N-alkylaminoalkoxy of 2-9 carbon atoms, N,N-dialkylaminoalkoxy of 3-10 carbon atoms, mercapto, and benzoylamino;

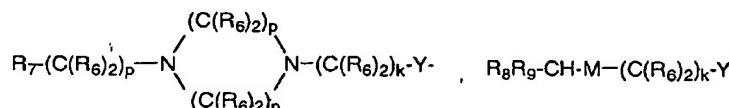
15 10 Z is -NH-, -O-, -S-, or -NR- ;
R is alkyl of 1-6 carbon atoms, or carboalkyl of 2-7 carbon atoms;

20 25 G₁, G₂, R₁, and R₄ are each, independently, hydrogen, halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkenyloxy of 2-6 carbon atoms, alkynyloxy of 2-6 carbon atoms, hydroxymethyl, halomethyl, alkanoyloxy of 1-6 carbon atoms, alkenoyloxy of 3-8 carbon atoms, alkynoyloxy of 3-8 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkenoyloxymethyl of 4-9 carbon atoms, alkynoyloxymethyl of 4-9 carbon atoms, alkoxyymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, alkylsulphanyl of 1-6 carbon atoms, alkylsulphonyl of 1-6 carbon atoms, alkylsulfonamido of 1-6 carbon atoms, alkenylsulfonamido of 2-6 carbon atoms, alkynylsulfonamido of 2-6 carbon atoms, hydroxy, trifluoromethyl, trifluoromethoxy, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzyl, amino, hydroxyamino, alkoxyamino of 1-4 carbon atoms, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, N-alkylcarbamoyl, N,N-dialkylcarbamoyl, N-alkyl-N-alkenylamino of 4 to 12 carbon atoms, N,N-dialkenylamino of 6-12 carbon atoms, phenylamino, benzylamino,

30 35 40 45 50 55

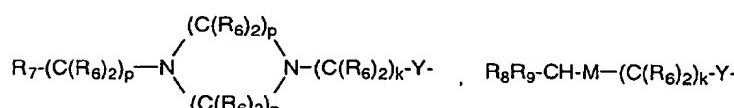
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$R_7-(C(R_6)_2)_n-Y-$, $R_7-(C(R_6)_2)_p-M-(C(R_6)_2)_q-Y-$, or $Het-(C(R_6)_2)_n-W-(C(R_6)_2)_k-Y-$

15 with the proviso that either G₁ or G₂ or both G₁ and G₂ must be a radical selected from the group



25 R₇-{C(R₆)₂}_n-Y- . . . R₇-{C(R₆)₂}_n-M-(C(R₆)₂)_k-Y- . . . Het-(C(R₆)₂)_l-W-(C(R₇)₂)_m-Y-

$$5 \quad \text{or} \quad R_2-N-H \quad ;$$

30 Y is a divalent radical selected from the group consisting of

$-(CH_2)_a-$, $-O-$, and $-N-$

35 10 R₇ is -NR₆R₆, -J, -OR₆, -N(R₆)₃ or -NR₆(OR₆):

R₇' is -NR₆(OR₆), -N(R₆)₃, alkoxy of 1-6 carbon atoms, alkynoxy of 1-6 carbon

40 atoms, N-alkyl-N-alkenylamino of 4 to 12 carbon atoms, N,N-dialkenylamino of 6-12 carbon atoms, N-alkyl-N-alkynylamino of 4 to 12 carbon atoms, N-alkenyl-N-

15 alkylnylamino or 4 to 12 carbon atoms, or N,N-dialkynylamino of 6-12 carbon atoms
with the proviso that the alkenyl or alkynyl moiety is bound to a nitrogen or oxygen
atom through a saturated carbon atom;

M is $>\text{NR}_6$, $-\text{O}-$, $>\text{N}-(\text{C}(\text{R}_6)_2)_p\text{NR}_6\text{R}_6$, or $>\text{N}-(\text{C}(\text{R}_6)_2)_p-\text{OR}_6$

W is $\geq N\beta \epsilon_{-} - \Omega_{-}$ or is a bond

50 20 Het is a heterocycle selected from the group consisting of morpholine, thiomorpholine, thiomorpholine S-oxide, thiomorpholine S,S-dioxide

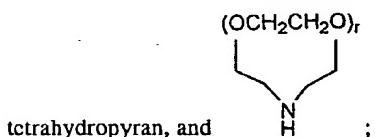
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10 piperidine, pyrrolidine, aziridine, pyridine, imidazole, 1,2,3-triazole, 1,2,4-triazole, thiazole, thiazolidine, tetrazole, piperazine, furan, thiophene, tetrahydrothiophene, tetrahydrofuran, dioxane, 1,3-dioxolane,

15



20

5 wherein the heterocycle is optionally mono- or di-substituted on carbon or nitrogen with R₆, optionally mono- or di-substituted on carbon with hydroxy, -N(R₆)₂, or -OR₆, optionally mono or di-substituted on carbon with the mono-valent radicals -(C(R₆)₂)_sOR₆ or -(C(R₆)₂)_sN(R₆)₂, or optionally mono or di-substituted on a saturated carbon with divalent radicals -O- or -O(C(R₆)₂)_sO-;

25

30 R₆ is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 1-6 carbon atoms, carboalkyl of 2-7 carbon atoms, carboxyalkyl (2-7 carbon atoms), phenyl, or phenyl optionally substituted with one or more halogen, alkoxy of 1-6 carbon atoms, trifluoromethyl, amino, alkylamino of 1-3 carbon atoms, dialkylamino of 2-6 carbon atoms, nitro, cyano, azido, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, carboxyl, carboalkoxy of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, or alkyl of 1-6 carbon atoms;

35

40 R₂, is selected from the group consisting of

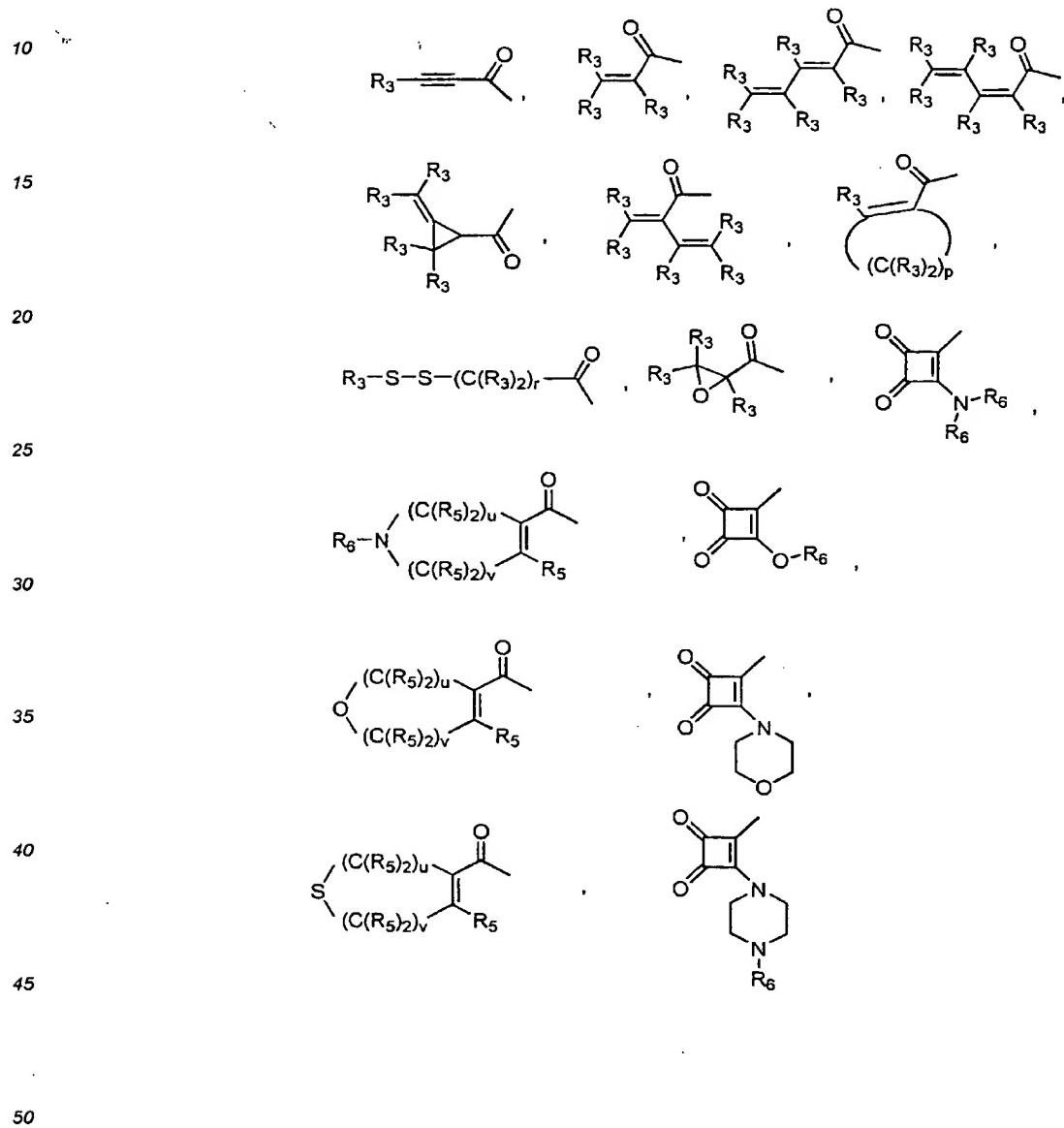
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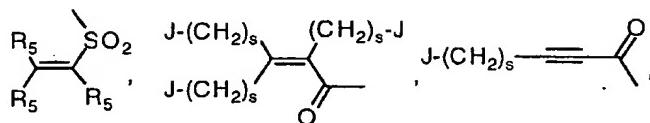


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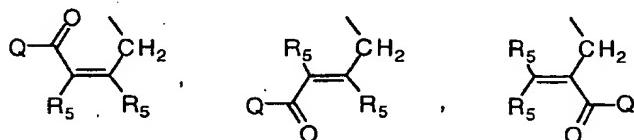
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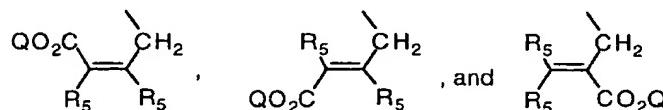
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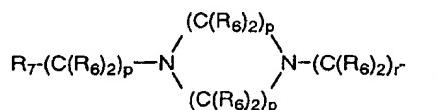


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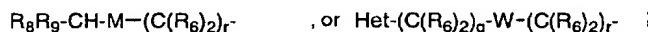
R₃ is independently hydrogen, alkyl of 1-6 carbon atoms, carboxy, carboalkoxy of 1-

5 6 carbon atoms, phenyl, carboalkyl of 2-7 carbon atoms,

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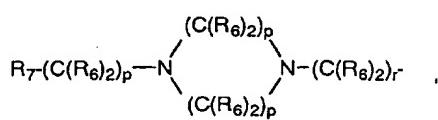
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with the proviso that at least one of the R₃ groups is selected from the group

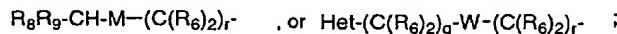
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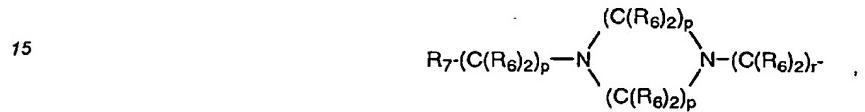


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10 R₅ is independently hydrogen, alkyl of 1-6 carbon atoms, carboxy, carboalkoxy of 1-6 carbon atoms, phenyl, carboalkyl of 2-7 carbon atoms,



20 5 R₈R₉-CH-M-(C(R₆)₂)_r ; or Het-(C(R₆)₂)_q-W-(C(R₆)₂)_r ;

25 R₈, and R₉ are each, independently, -(C(R₆)₂)_rNR₆R₆, or -(C(R₆)₂)_rOR₆;

30 10 J is independently hydrogen, chlorine, fluorine, or bromine;

10 10 Q is alkyl of 1-6 carbon atoms or hydrogen;

30 a = 0 or 1;

g = 1-6;

k = 0-4;

n is 0-1;

35 15 p = 2-4;

q=0-4;

r = 1-4;

s = 1-6;

40 40 u = 0-4 and v = 0-4 , wherein the sum of u+v is 2-4;

20 20 or a pharmaceutically acceptable salt thereof,

provided that

45 when R₆ is alkenyl of 2-7 carbon atoms or alkynyl of 2-7 carbon atoms, such alkenyl or alkynyl moiety is bound to a nitrogen or oxygen atom through a saturated carbon atom;

50 25 and further provided that

when Y is -NR₆- and R₇ is -NR₆R₆, -N(R₆)₃⁺, or -NR₆(OR₆), then g = 2-6;

55

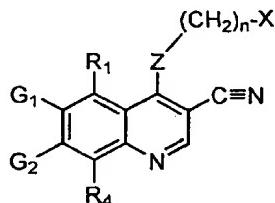
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- when M is -O- and R₇ is -OR₆, then p = 1-4;
- 10 when Y is -NR₆-, then k = 2-4;
- when Y is -O- and M or W is -O-, then k = 1-4
- 15 when W is not a bond with Het bonded through a nitrogen atom, then q = 2-4
- 5 and when W is a bond with Het bonded through a nitrogen atom and Y is -O- or -NR₆-, then k = 2-4.

20 9. A pharmaceutical composition which comprises a compound of formula 1 having the structure

25



1

30

wherein:

X is cycloalkyl of 3 to 7 carbon atoms, which may be optionally substituted with one or more alkyl of 1 to 6 carbon atom groups; or is a pyridinyl, pyrimidinyl, or phenyl ring wherein the pyridinyl, pyrimidinyl, or phenyl ring may be 35 optionally mono-, di-, or tri-substituted with a substituent selected from the group consisting of halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxyalkyl of 2-7 carbon atoms, alkanoyloxyalkyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, 40 hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 15 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, carboxyalkyl of 2-7 carbon atoms, carboalkoxyalkyl of 3-8 carbon atoms, 45 50 55

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atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-10 carbon atoms, N-alkylaminoalkoxy of 2-9 carbon atoms, N,N-dialkylaminoalkoxy of 3-10 carbon atoms, mercapto, and benzoylamino;

10 5 Z is -NH-, -O-, -S-, or -NR- ;
 R is alkyl of 1-6 carbon atoms, or carboalkyl of 2-7 carbon atoms;

15 10 G₁, G₂, R₁, and R₄ are each, independently, hydrogen, halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkenyloxy of 2-6 carbon atoms, alkynyoxy of 2-6 carbon atoms, hydroxymethyl, halomethyl, alkanoyloxy of 1-6 carbon atoms, alkenoyloxy of 3-8 carbon atoms, alkynoyloxy of 3-8 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkenoyloxymethyl of 4-9 carbon atoms, alkynoyloxymethyl of 4-9 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, alkylsulphinyl of 1-6 carbon atoms, alkylsulphonyl of 1-6 carbon atoms, alkylsulfonamido of 1-6 carbon atoms, alkenylsulfonamido of 2-6 carbon atoms, alkynylsulfonamido of 2-6 carbon atoms, hydroxy, trifluoromethyl, trifluoromethoxy, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzyl, amino, hydroxyamino, alkoxyamino of 1-4 carbon atoms, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, N-alkylcarbamoyl, N,N-dialkylcarbamoyl, N-alkyl-N-alkenylamino of 4 to 12 carbon atoms, N,N-dialkenylamino of 6-12 carbon atoms, phenylamino, benzylamino,

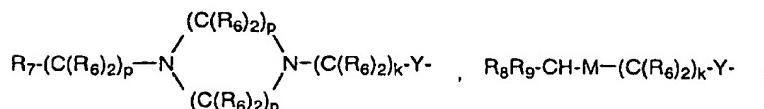
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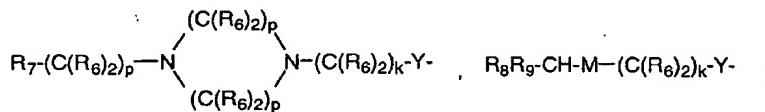


45 50 R₇-(C(R₆)₂)_q-Y- , R₇-(C(R₆)₂)_p-M-(C(R₆)₂)_k-Y- , or Het-(C(R₆)₂)_q-W-(C(R₆)₂)_k-Y-
 with the proviso that either G₁ or G₂ or both G₁ and G₂ must be a radical selected from the group

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15

 $\text{R}'_7-(\text{C}(\text{R}_6)_2)_q-\text{Y}$, $\text{R}_7-(\text{C}(\text{R}_6)_2)_p-\text{M}-(\text{C}(\text{R}_6)_2)_k-\text{Y}$, $\text{Het}-(\text{C}(\text{R}_6)_2)_q-\text{W}-(\text{C}(\text{R}_6)_2)_k-\text{Y}$,

or $\text{R}_2-\overset{\text{H}}{\underset{|}{\text{N}}}-$;

20

Y is a divalent radical selected from the group consisting of

5

 $-(\text{CH}_2)_a-$, $-\text{O}-$, and $-\overset{\text{H}}{\underset{\text{R}_6}{\text{N}}}-$;

25

R_7 is $-\text{NR}_6\text{R}_6$, $-\text{J}$, $-\text{OR}_6$, $-\text{N}(\text{R}_6)_3^+$, or $-\text{NR}_6(\text{OR}_6)$;

R'_7 is $-\text{NR}_6(\text{OR}_6)$, $-\text{N}(\text{R}_6)_3^+$, alkenoxy of 1-6 carbon atoms, alkynoxy of 1-6 carbon

10 atoms, N-alkyl-N-alkenylamino of 4 to 12 carbon atoms, N,N-dialkenylamino of 6-12 carbon atoms, N-alkyl-N-alkynylamino of 4 to 12 carbon atoms, N-alkenyl-N-alkynylamino of 4 to 12 carbon atoms, or N,N-dialkynylamino of 6-12 carbon atoms with the proviso that the alkenyl or alkynyl moiety is bound to a nitrogen or oxygen atom through a saturated carbon atom;

30

15 M is $>\text{NR}_6$, $-\text{O}-$, $>\text{N}-(\text{C}(\text{R}_6)_2)_p\text{NR}_6\text{R}_6$, or $>\text{N}-(\text{C}(\text{R}_6)_2)_p-\text{OR}_6$;

20 W is $>\text{NR}_6$, $-\text{O}-$ or is a bond;

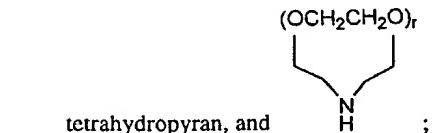
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25 Het is a heterocycle selected from the group consisting of morpholine, thiomorpholine, thiomorpholine S-oxide, thiomorpholine S,S-dioxide, piperidine, pyrrolidine, aziridine, pyridine, imidazole, 1,2,3-triazole, 1,2,4-triazole, thiazole, thiazolidine, tetrazole, piperazine, furan, thiophene,

40

30 tetrahydrothiophene, tetrahydrofuran, dioxane, 1,3-dioxolane,

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wherein the heterocycle is optionally mono- or di-substituted on carbon or
10 nitrogen with R₆, optionally mono- or di-substituted on carbon with hydroxy,
-N(R₆)₂, or -OR₆, optionally mono or di-substituted on carbon with the
mono-valent radicals -(C(R₆)₂)_sOR₆ or -(C(R₆)₂)_sN(R₆)₂, or optionally
15 mono or di-substituted on a saturated carbon with divalent radicals -O- or
-O(C(R₆)₂)_sO-;

20 R₆ is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-
6 carbon atoms, cycloalkyl of 1-6 carbon atoms, carboalkyl of 2-7 carbon
10 atoms, carboxyalkyl (2-7 carbon atoms), phenyl, or phenyl optionally
substituted with one or more halogen, alkoxy of 1-6 carbon atoms,
25 trifluoromethyl, amino, alkylamino of 1-3 carbon atoms, dialkylamino of 2-6
carbon atoms, nitro, cyano, azido, halomethyl, alkoxymethyl of 2-7 carbon
atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkylthio of 1-6 carbon
30 atoms, hydroxy, carboxyl, carboalkoxy of 2-7 carbon atoms, phenoxy, phenyl,
thiophenoxy, benzoyl, benzyl, phenylamino, benzylamino, alkanoylamino of
1-6 carbon atoms, or alkyl of 1-6 carbon atoms;

35 R₂ is selected from the group consisting of

20

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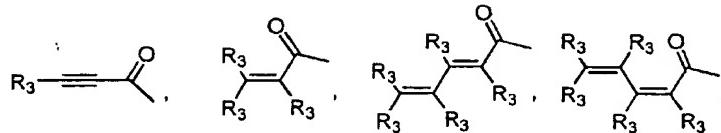
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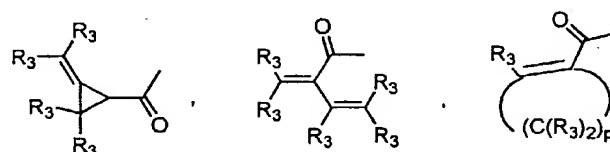
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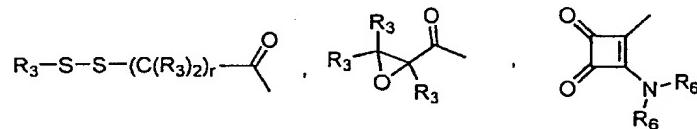
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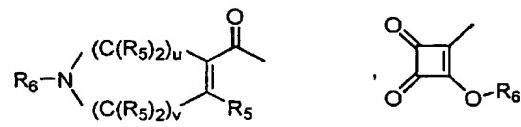
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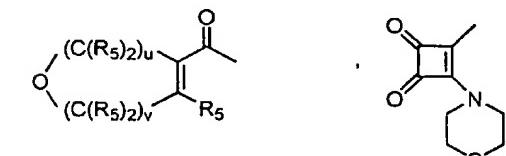
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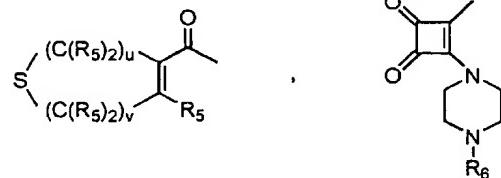
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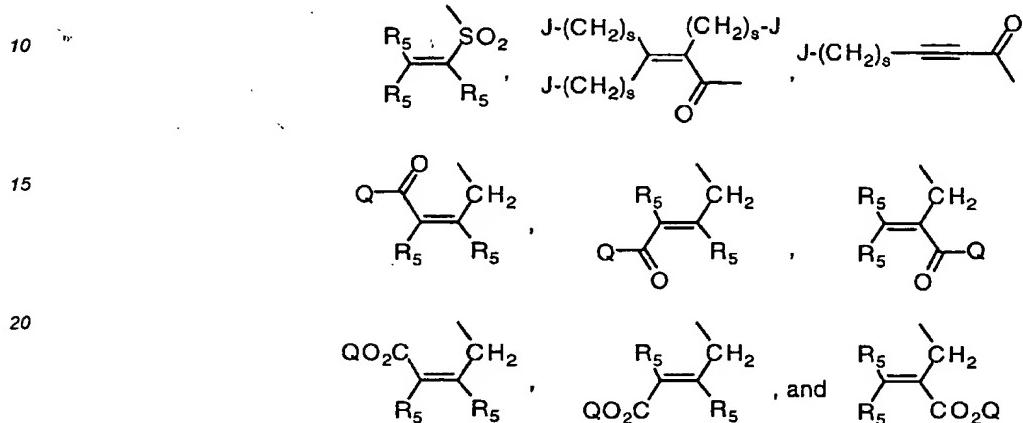
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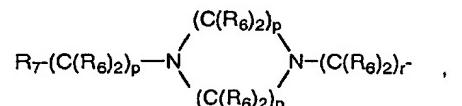
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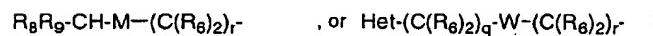
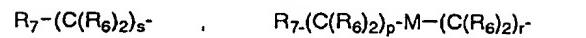
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R₃ is independently hydrogen, alkyl of 1-6 carbon atoms, carboxy, carboalkoxy or 1-6 carbon atoms, phenyl, carboalkyl of 2-7 carbon atoms.

30



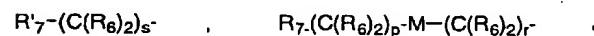
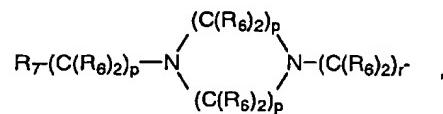
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with the proviso that at least one of the R₃ groups is selected from the group

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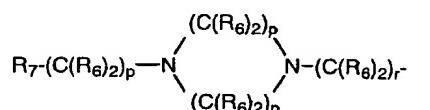


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10 R5 is independently hydrogen, alkyl of 1-6 carbon atoms, carboxy, carboalkoxy of
1-6 carbon atoms, phenyl, carboalkyl of 2-7 carbon atoms.



$$R_7-(C(R_6)_2)_5- \quad , \quad R_7-(C(R_6)_2)_5-M-(C(R_6)_2)_5$$

20 $R_8R_9\text{-CH-M-}(C(R_6)_2)_r$, or $\text{Het-}(C(R_6)_2)_q\text{-W-}(C(R_6)_2)_r$

R₈, and R₉ are each, independently, -(C(R₆)₂)_rNR₆R₆, or -(C(R₆)₂)_rOR₆

J is independently hydrogen, chlorine, fluorine, or bromine:

Q is alkyl of 1-6 carbon atoms or hydrogen:

10 a = 0 or 1;

g = 1-6:

$k = 0\text{--}4$:

n is 0-1:

$n = 2-4$:

15 $a=0\text{--}4$

T = 1.4

S = 1.6

11 = 0.4

or a pharmaceutically acceptable salt thereof.

provided that

26 provided that

when R₆ is alketyl of 2-7 carbon atoms or alkynyl of 2-7 carbon atoms, such

alkenyl or alkynyl moiety is bound to a nitrogen or oxygen atom through a saturated carbon atom;

and further provided that

when M is -O- and R₇ is -OR₆, then p = 1-4;

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when Y is -NR₆-, then k = 2-4;

when Y is -O- and M or W is -O-, then k = 1-4;

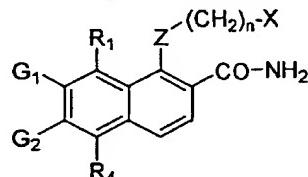
when W is not a bond with Het bonded through a nitrogen atom, then q = 2-4;

and when W is a bond with Het bonded through a nitrogen atom and Y is -O- or

5 -NR₆-, then k = 2-4.

10. A process for preparing a compound of formula 1 or a pharmaceutically acceptable salt therof which comprises

20 (a) reacting a compound having the formula



25 10 where R₁, G₁, G₂, R₄, Z, n and X are as defined above with a dehydrating agent so as to convert the aminocarbonyl group into a cyano group, or

30 (b) reacting a compound having the formula



35 15 or a salt thereof with a compound having the formula



40 where Q is a leaving group and A₁, A₂ and A₃ are such that A₁-NA₂-A₃ is a compound conforming with formula 1; or

(c) reacting a compound having the formula



45 or a salt thereof with a compound having the formula



where Q is as defined above and A₄ and A₅ are such that A₄-O-A₅ is a compound conforming with formula 1; or

50 25 (d) adding an acid to a compound having formula 1 so that an acid addition salt is prepared.

INTERNATIONAL SEARCH REPORT

Int'l. Application No
PCT/US 99/22056

A. CLASSIFICATION OF SUBJECT MATTER		
IPC 7 C07D215/54 A61K31/47 C07D401/12 C07D417/12 C07D215/56 C07D401/04 C07D491/10 C07D405/12 C07D413/12 //(C07D491/10, 317:00, 211:00)		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07D A61K.		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 02437 A (GLAXO GROUP LTD.) 22 January 1998 (1998-01-22) page 1; claim 1	1,9
A	EP 0 787 722 A (AMERICAN CYANAMID COMPANY) 6 August 1997 (1997-08-06) page 3, line 1 - line 8; claim 1	1,9
A	WO 96 09294 A (THE WELLCOME FOUNDATION LTD.) 28 March 1996 (1996-03-28) page 5; claim 1	1,9
P,X	WO 98 43960 A (AMERICAN CYANAMID COMPANY) 8 October 1998 (1998-10-08) complete document	1,9
<input type="checkbox"/> Further documents are listed in the continuation of box C.		<input checked="" type="checkbox"/> Patent family members are listed in annex.
* Special categories of cited documents : *A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed		
Date of the actual completion of the international search 17 January 2000		Date of mailing of the international search report 26/01/2000
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax. (+31-70) 340-3016		Authorized officer Van Bijlen, H

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/22056

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 6-8 because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 6-8 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int'l Application No
PCT/US 99/22056

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